STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 153170

TO: Rei-Tsang Shiao **Location: 5a10 / 5c18** **Thursday, May 12, 2005** **Art Unit: 1626** **Phone: 571-272-0707** **Serial Number: 10 / 660775**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Remsen 1a51** **Phone: 571-272-2504** **jan.delaval@uspto.gov**

Search Notes

Access DB# 153170

Jan Delaval for search

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Robert (Reby) Shiao Examiner #: 79521 Date: 5/12/05

Art Unit: 1626 Phone Number ~~22~~ 2-0707 Serial Number: 10/660775

Mail Box and Bldg/Room Location: 5A70/5C18 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

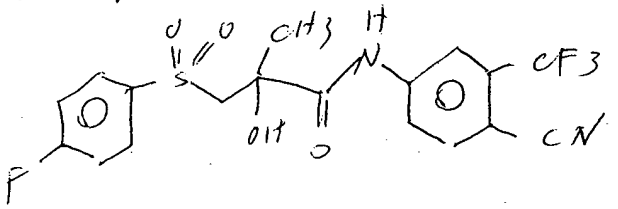
Title of invention: Bicalutamide form

Inventors (please provide full names): Westhem.

Earliest Priority Filing Date: _____

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

I search cpd I. (bicalutamide)



II search polymorphism (i.e. amphorphus or crystalline form) of cpd I

III ~~process for making~~ method of use or preparation for making of crystalline bicalutamide

****

STAFF USE ONLY		Type of Search		Vendors and cost where applicable	
Searcher	Jan	NA Sequence (#)		STN	✓
Searcher Phone #	22504	AA Sequence (#)		Dialog	
Searcher Location		Structure (#)	✓	Questel/Orbit	
Date Searcher Picked Up	5/12/05	Bibliographic		Dr.Link	
Date Completed	5/12/05	Litigation		Lexis/Nexis	
Searcher Prep & Review Time		Fulltext		Sequence Systems	
Clerical Prep Time	15	Patent Family		WWW/Internet	
Online Time	+60	Other		Other (specify)	

PTO-1590 (8-01)

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 08:51:02 ON 12 MAY 2005
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   11 MAY 2005  HIGHEST RN 850303-40-1
DICTIONARY FILE UPDATES:  11 MAY 2005  HIGHEST RN 850303-40-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*************************************************************************
*                                                                       *
* The CA roles and document type information have been removed from     *
* the IDE default display format and the ED field has been added,       *
* effective March 20, 2005.  A new display format, IDERL, is now        *
* available and contains the CA role and document type information.     *
*                                                                       *
*************************************************************************

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can tot l3

L3   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   113299-40-4  REGISTRY
ED   Entered STN:  12 Mar 1988
CN   Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
     fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI)   (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
     fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (R)-
OTHER NAMES:
CN   (R)-Bicalutamide
CN   (R)-Casodex
FS   STEREOSEARCH
MF   C18 H14 F4 N2 O4 S
SR   CA
LC   STN Files:   BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, IMSPATENTS,
       IMSRESEARCH, PS, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.  Rotation (-).
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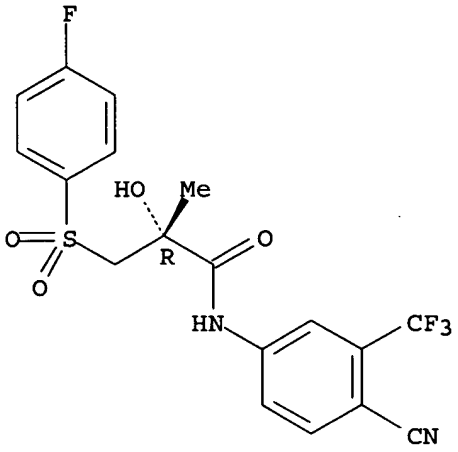


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

26 REFERENCES IN FILE CA (1907 TO DATE)
26 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:309184

REFERENCE 2: 141:184591

REFERENCE 3: 140:303414

REFERENCE 4: 139:375064

REFERENCE 5: 138:406952

REFERENCE 6: 138:343868

REFERENCE 7: 138:321017

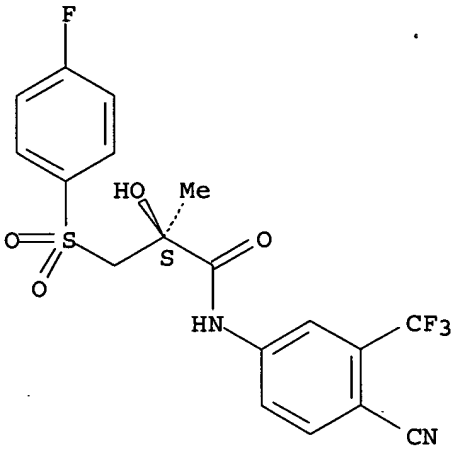
REFERENCE 8: 138:24551

REFERENCE 9: 137:384623

REFERENCE 10: 137:284397

L3 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN 113299-38-0 REGISTRY
ED Entered STN: 12 Mar 1988
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (S)-
OTHER NAMES:
CN (S)-Casodex
FS STEREOSEARCH
MF **C18 H14 F4 N2 O4 S**
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSPATENTS, IMSRESEARCH, PS, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1907 TO DATE)
15 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:309184

REFERENCE 2: 141:184591

REFERENCE 3: 138:24551

REFERENCE 4: 137:384623

REFERENCE 5: 136:79780

REFERENCE 6: 134:326279

REFERENCE 7: 134:86040

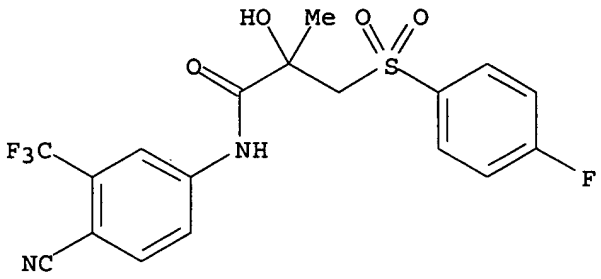
REFERENCE 8: 133:12739

REFERENCE 9: 130:49289

REFERENCE 10: 127:242768

L3 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN 90357-06-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (±)-
OTHER NAMES:
CN (±)-4'-Cyano-α,α,α-trifluoro-3-[(p-fluorophenyl)sulfonyl]-2-methyl-m-lactotoluidide
CN **Bicalutamide**
CN Casodex
CN Cosudex
CN ICI 176334
CN ZD 176334

DR 151262-58-7
MF **C18 H14 F4 N2 O4 S**
LC STN Files: ADISINSIGHT, ADISNEWS, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

437 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
440 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:366650

REFERENCE 2: 142:349042

REFERENCE 3: 142:310099

REFERENCE 4: 142:309898

REFERENCE 5: 142:309871

REFERENCE 6: 142:291460

REFERENCE 7: 142:291364

REFERENCE 8: 142:290711

REFERENCE 9: 142:273618

REFERENCE 10: 142:273482

=> d his

(FILE 'HOME' ENTERED AT 08:12:56 ON 12 MAY 2005)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 08:13:05 ON 12 MAY 2005
E BICALUTAMIDE/CN
L1 1 S E3
E C18H14F4N2O4S/MF
L2 3 S E3 AND 2/NR

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L3            3 S L1,L2
                SEL RN
L4            0 S E1-E3/CRN

     FILE 'HCAPLUS' ENTERED AT 08:14:50 ON 12 MAY 2005
L5          452 S L3
L6          581 S BICALUTAMID? OR CASODEX OR ICI176334 OR ZD176334 OR (ICI OR Z
L7          594 S L5,L6
L8            2 S L7 AND CRYS?/SC,SX
L9           16 S L7 AND ?CRYS?
L10           8 S L7 AND POLYMORPH?
                E POLYMORPH/CT
L11           3 S L7 AND (E19+OLD,NT,PFT,RT OR E20+OLD,NT,PFT,RT)
L12           1 S L7 AND E19-E29
                E E20+ALL
L13           9 S L7 AND (E13+OLD,NT,PFT,RT OR E14+OLD,NT,PFT,RT OR E15+OLD,NT,
                E E1+ALL
L14          12 S L7 AND E1+OLD,NT,PFT,RT
L15          27 S L7 AND (E396+OLD,NT,PFT,RT OR E397+OLD,NT,PFT,RT OR E398+OLD,
L16          55 S L7 AND (E405+OLD,NT,PFT,RT OR E411+OLD,NT,PFT,RT OR E412+OLD,
                E CRYSTALLIN/CT
L17           0 S L7 AND E10-E13
L18           0 S L7 AND E7+OLD,NT,PFT,RT
                E L7 AND E14+OLD,NT,PFT,RT
                E CRYSTALLIN/CT
L19           0 S L7 AND (E14+OLD,NT,PFT,RT OR E45+NT,PFT,RT)
L20           6 S L7 AND E49+OLD,NT,PFT,RT
L21           6 S L7 AND (E85+OLD,NT,PFT,RT OR E88+OLD,NT,PFT,RT OR E91+OLD,NT,
L22          79 S L8-L21
L23           1 S US20040063782/PN OR (US2003-660775# OR US2003-470223# OR US20
                E WESTHEIM R/AU
L24           2 S E4,E5
                E SYNTHON/PA,CS
L25          62 S E3-E32
L26           3 S L23-L25 AND L7
L27           2 S L26 AND L22
L28           1 S L26 NOT L27
L29           3 S L27,L28
                E PULVERIZ/CT
L30           2 S L7 AND E4+OLD,NT,PFT,RT
                E GRANULATION/CT
L31           2 S L7 AND E3+OLD,NT,PFT,RT
                E E14+ALL
L32          80 S L30,L31,L22
L33           2 S L7 AND ?AMORPH?
                E AMORPH/CT
L34           5 S L7 AND (E15+OLD,NT,PFT,RT OR E22+OLD,NT,PFT,RT)
L35           5 S L7 AND E150+OLD,NT,PFT,RT
L36           0 S L7 AND (E161+OLD,NT,PFT,RT OR E162+OLD,NT,PFT,RT OR E163+OLD,
L37          80 S L32-L35
L38           2 S L23-L25 AND L37
L39           3 S L29,L38
L40          50 S L37 AND (PD<=20020927 OR PRD<=20020927 OR AD<=20020927)
L41          49 S L40 NOT L39
L42          52 S L3(L)PREP+NT/RL OR L3(L)PROC+NT/RL OR L3/P
L43          10 S L41 AND L42
L44           4 S L43 AND CRYS?
L45           2 S L44 AND CRYS?/TI
L46           5 S L39,L45
L47          39 S L41 NOT L42-L46
                SEL DN AN 7 22
L48           2 S L47 AND E1-E6
L49           7 S L46,L48
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L50          19 S L7 AND RACEM?
L51          16 S L50 AND (PD<=20020927 OR PRD<=20020927 OR AD<=20020927)
L52          14 S L51 NOT L49
                SEL DN AN 2 4 5
L53           3 S E7-E13 AND L52
L54          10 S L49,L53 AND L5-L53
L55           7 S L7 AND (ETHYLACETATE OR ETHYL ACETATE OR ETOAC)

     FILE 'REGISTRY' ENTERED AT 08:44:11 ON 12 MAY 2005
L56           1 S 141-78-6

     FILE 'HCAPLUS' ENTERED AT 08:44:16 ON 12 MAY 2005
L57           6 S L7 AND L56
L58           7 S L55,L57
L59           4 S L58 AND L54
L60          10 S L54,L59
L61           3 S L58 NOT L60
                SEL DN AN 1
L62           1 S E14-E16 AND L61
L63          11 S L60,L62

     FILE 'REGISTRY' ENTERED AT 08:45:48 ON 12 MAY 2005
L64           1 S 63-42-3
L65           1 S 9004-65-3
L66           1 S 9005-25-8
L67           1 S 10103-46-5
L68           1 S 9004-34-6
L69          13 S 7664-38-2/CRN AND CA/ELS AND 2/NC NOT (MXS OR PMS OR IDS OR M
L70          11 S L69 NOT 45CA?
L71        6830 S 9004-34-6/CRN
L72        2208 S 9005-25-8/CRN

     FILE 'HCAPLUS' ENTERED AT 08:48:07 ON 12 MAY 2005
L73          14 S L64-L68,L70-L72 AND L7
L74          10 S L73 AND (PD<=20020927 OR PRD<=20020927 OR AD<=20020927)
L75           1 S L74 AND L63
L76          11 S L63,L75
L77           9 S L74 NOT L76
                SEL DN AN 2 3 4 5
L78           4 S L77 AND E17-E28
L79          15 S L76,L78 AND L5-L55,L57-L63,L73-L78

     FILE 'REGISTRY' ENTERED AT 08:51:02 ON 12 MAY 2005

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 08:51:15 ON 12 MAY 2005
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FILE COVERS 1907 - 12 May 2005  VOL 142 ISS 20
FILE LAST UPDATED: 11 May 2005  (20050511/ED)
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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l79 all hitstr tot

L79 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2005:99457** HCAPLUS
DN **142:176567**
ED Entered STN: 04 Feb 2005
TI **Crystallization** process for purifying and isolating **racemic bicalutamide**
IN Dolitzky, Ben-Zion; Reany, Ofer; Shammai, Jenny
PA Biogal Gyogyszergyar Rt., Hung.; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C315-06
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 48
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005009946	A1	20050203	WO 2003-US20307	20030625

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI WO 2003-US20307 20030625
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2005009946	ICM	C07C315-06

AB A process for the purification and isolation of **bicalutamide** by solution **crystallization** comprises: (i) combining crude **bicalutamide** and a solvent; (ii) **crystallizing** the **bicalutamide** from the solvent; and (iii) collecting the **crystals** of **bicalutamide.**
ST **bicalutamide racemic crystn**
IT **Crystallization**
(**crystallization** process for purifying and isolating **racemic bicalutamide**)
IT **Precipitation (chemical)**
(in a **crystallization** process for purifying and isolating **racemic bicalutamide**)
IT **90357-06-5P, Bicalutamide**
RL: **PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)**
(**crystallization** process for purifying and isolating **racemic bicalutamide**)
IT 60-29-7, Diethyl ether, uses 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, 2-Propanol, uses 67-64-1, Acetone, uses 67-66-3, Chloroform, uses 67-68-5, Dmso, uses 68-12-2, Dmf, uses 71-23-8,

1-Propanol, uses 75-05-8, Acetonitrile, uses 75-09-2, Dichloromethane, uses 107-06-2, 1,2-Dichloroethane, uses 108-10-1, Mibk 108-88-3, Toluene, uses 109-99-9, THF, uses 110-54-3, Hexane, uses **141-78-6, Ethyl acetate**, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; **crystallization** process for purifying and isolating **racemic bicalutamide**)

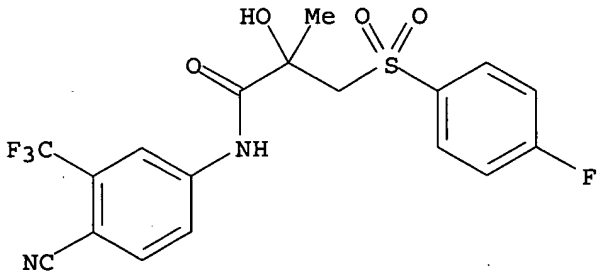
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Brlik, J; WO 0100608 A 2001 HCAPLUS
(2) Helm Ag; WO 03097590 A 2003 HCAPLUS
(3) Itaya, N; US 2003191337 A1 2003 HCAPLUS
(4) Sund; WO 0224638 A 2002 HCAPLUS
(5) Tucker, H; US 4636505 A 1987 HCAPLUS
(6) Tucker, H; JOURNAL OF MEDICINAL CHEMISTRY 1988, V31(5), P954 HCAPLUS

IT **90357-06-5P, Bicalutamide**
RL: **PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)**
(**crystallization** process for purifying and isolating **racemic bicalutamide**)

RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



IT **141-78-6, Ethyl acetate**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; **crystallization** process for purifying and isolating **racemic bicalutamide**)

RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)

Et—O—Ac

L79 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:1015874 HCAPLUS
DN 141:416055
ED Entered STN: 25 Nov 2004
TI **Bicalutamide** forms, compositions, and processes thereof
IN Siles Ortega, Arturo; Cucala Escoi, Joan
PA **Synthon B.V., Neth.**
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-277

ICS A61K009-16; A61K009-48; A61K009-20; A61P013-08
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004100944	A1	20041125	WO 2004-EP5189	20040513
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005008691	A1	20050113	US 2004-842632	20040511
PRAI US 2003-470224P	P	20030514		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004100944	ICM	A61K031-277
	ICS	A61K009-16; A61K009-48; A61K009-20; A61P013-08
WO 2004100944	ECLA	A61K009/16H4B; A61K009/16H6; A61K009/16H6F; A61K009/20H4; A61K009/20H4B; A61K009/20H6B
US 2005008691	NCL	424/451.000; 424/464.000; 514/522.000
	ECLA	A61K009/16H4B; A61K009/16H6; A61K009/16H6F; A61K009/20H4; A61K009/20H4B; A61K009/20H6B; A61K031/277

AB A **bicalutamide** pharmaceutical composition having a high content of **bicalutamide** is provided. The composition can be made from micronized **bicalutamide**, in order to enhance the speed of dissoln. and is preferably made from a granulate of **bicalutamide** that contains at least 50 (weight/weight)% of **bicalutamide.**

ST **bicalutamide** micronized granulate formulation

IT Binders
Compaction
Crystal morphology
Crystallization
Dissolution
Drug bioavailability
Granulation
Milling (size reduction)
Particle size distribution
Surfactants
Wetting agents
(**bicalutamide** forms, compns., and processes for their manufacture)

IT Drug delivery systems
(capsules; **bicalutamide** forms, compns., and processes for their manufacture)

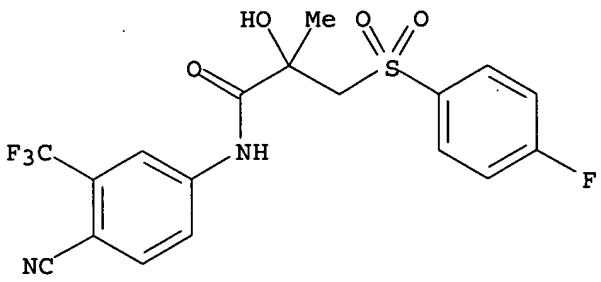
IT Drug delivery systems
(carriers; **bicalutamide** forms, compns., and processes for their manufacture)

IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(esters; **bicalutamide** forms, compns., and processes for their manufacture)

IT **Pulverization**
(micronization; **bicalutamide** forms, compns., and processes for their manufacture)

IT Solvents
(organic, absence of; **bicalutamide** forms, compns., and processes for their manufacture)

IT Drug delivery systems
(tablets; **bicalutamide** forms, compns., and processes for their manufacture)
IT **Granulation**
(wet; **bicalutamide** forms, compns., and processes for their manufacture)
IT **90357-06-5P, Bicalutamide**
RL: **PEP (Physical, engineering or chemical process)**; **PUR (Purification or recovery)**; **PYP (Physical process)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; **PROC (Process)**; USES (Uses)
(**bicalutamide** forms, compns., and processes for their manufacture)
IT 9003-39-8, Polyvinylpyrrolidone
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bicalutamide** forms, compns., and processes for their manufacture)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Astrazeneca Uk Ltd; WO 02080902 A 2002 HCAPLUS
(2) Bateman, N; WO 02067893 A 2002 HCAPLUS
(3) Fo; WO 2004009057 A 2004 HCAPLUS
(4) Hugh, C; WO 03043630 A 2003 HCAPLUS
(5) Sepracor Inc; WO 9519770 A 1995 HCAPLUS
(6) Systhon Bv; WO 2004029021 A 2004 HCAPLUS
IT **90357-06-5P, Bicalutamide**
RL: **PEP (Physical, engineering or chemical process)**; **PUR (Purification or recovery)**; **PYP (Physical process)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; **PROC (Process)**; USES (Uses)
(**bicalutamide** forms, compns., and processes for their manufacture)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



L79 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:269869 HCAPLUS
DN 140:292649
ED Entered STN: 02 Apr 2004
TI **Bicalutamide polymorphic** forms
IN **Westheim, Raymond J. H.**
PA Neth.
SO U.S. Pat. Appl. Publ., 15 pp., which
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-277
INCL 514522000; 558410000
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004063782	A1	20040401	US 2003-660775	20030912 <--
	WO 2004029021	A1	20040408	WO 2003-EP10933	20030925 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-413765P P 20020927 <--
US 2003-470223P P 20030514 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004063782	ICM	A61K031-277
	INCL	514522000; 558410000
US 2004063782	NCL	514/522.000; 558/410.000
	ECLA	C07C317/46 <--

AB A new **crystalline** form of **bicalutamide** (form II) is disclosed. **Bicalutamide** form II is useful as a pharmaceutical and has antiandrogenic activity. A suspension of **bicalutamide** (1.0 g) in 25 mL **EtOAc** was refluxed until a clear solution was obtained. The solution was cooled down to 40° and mixed with 100 mL petroleum ether. During the addition, precipitation/**crystallization** of **bicalutamide** took place. The suspension was filtered and the solid material was then divided into 2 portions. One portion was dried at room temperature and the other portion was dried at 60°. According to DSC, IR, and x-ray, both portions are present as pure form II, and the drying temperature did not have any effect on the present **crystalline** form.

ST **bicalutamide polymorphic** form

IT Androgens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiandrogens; **bicalutamide polymorphic** forms)

IT **Crystal morphology**
Crystal structure
Polymorphism (crystal)
(**bicalutamide** forms)

IT Drug delivery systems
(solids, oral; **bicalutamide** forms)

IT Drug delivery systems
(solns.; **bicalutamide** forms)

IT Drug delivery systems
(suspensions; **bicalutamide** forms)

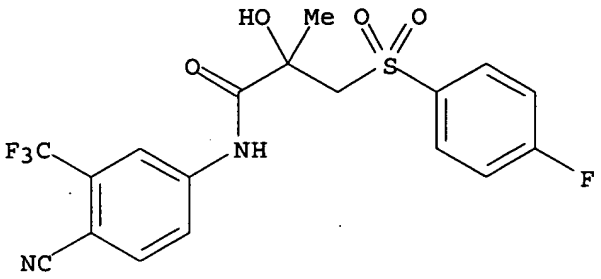
IT **90357-06-5, Bicalutamide**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bicalutamide** forms)

IT **63-42-3**, Lactose **9004-65-3**, Hydroxypropyl methylcellulose **9005-25-8**, Starch, biological studies **10103-46-5**, Calcium phosphate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bicalutamide** forms)

IT **9004-34-6**, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**microcryst.**; **bicalutamide** forms)

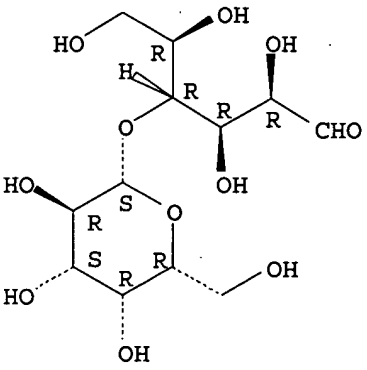
IT **90357-06-5, Bicalutamide**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**bicalutamide** forms)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



IT **63-42-3**, Lactose **9004-65-3**, Hydroxypropyl methylcellulose **9005-25-8**, Starch, biological studies **10103-46-5**, Calcium phosphate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bicalutamide** forms)
RN 63-42-3 HCAPLUS
CN D-Glucose, 4-O-β-D-galactopyranosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 9004-65-3 HCAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

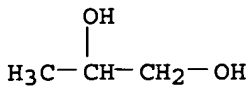
CM 2

CRN 67-56-1
CMF C H4 O

H_3C-OH

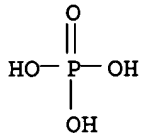
CM 3

CRN 57-55-6
CMF C3 H8 O2



RN 9005-25-8 HCAPLUS
CN Starch (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 10103-46-5 HCAPLUS
CN Phosphoric acid, calcium salt (8CI, 9CI) (CA INDEX NAME)



●x Ca

IT **9004-34-6**, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**microcryst.**; **bicalutamide** forms)
RN 9004-34-6 HCAPLUS
CN Cellulose (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L79 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:182593 HCAPLUS
DN 140:235504
ED Entered STN: 05 Mar 2004
TI Preparation and **crystallization** of **bicalutamide**
IN Dolitzky, Ben-Zion; Reany, Ofer; Shammai, Jenny
PA Israel
SO U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No. 170,721.
CODEN: USXXCO
DT Patent
LA English
IC ICM C07C317-28
INCL 564162000
CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 63
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004044249	A1	20040304	US 2003-606403	20030625 <--
	US 2003045741	A1	20030306	US 2002-170721	20020613 <--
	US 6737550	B2	20040518		
	US 2004059147	A1	20040325	US 2003-668982	20030922 <--
	US 6797843	B2	20040928		
	US 2004167349	A1	20040826	US 2004-791468	20040301 <--

	US 2004176633	A1	20040909	US 2004-796313	20040308	<--
	US 6861557	B2	20050301			
	US 2004176638	A1	20040909	US 2004-796822	20040308	<--
	US 6849763	B2	20050201			
	US 2005090682	A1	20050428	US 2004-994267	20041123	<--
PRAI	US 2001-298009P	P	20010613	<--		
	US 2002-371069P	P	20020409	<--		
	US 2002-170721	A2	20020613	<--		
	US 2004-791468	A3	20040301			
	US 2004-796313	A3	20040308			
	US 2004-796822	A3	20040308			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
US 2004044249	ICM	C07C317-28	
	INCL	564162000	
US 2004044249	NCL	564/162.000	
	ECLA	C07C255/58; C07D301/20; C07C315/04; C07C317/14; C07C319/14	<--
US 2003045741	NCL	568/028.000	
	ECLA	C07C255/58; C07C315/04; C07C317/14; C07C319/14; C07D301/20	<--
US 2004059147	NCL	568/028.000	
	ECLA	C07C255/58; C07C315/04; C07C317/14; C07C319/14; C07D301/20	<--
US 2004167349	NCL	558/413.000; 560/011.000	
	ECLA	C07C255/58; C07C315/04; C07C317/14; C07C319/14; C07D301/20	<--
US 2004176633	NCL	560/011.000; 568/028.000	
	ECLA	C07C255/58; C07C315/04; C07C317/14; C07C319/14; C07D301/20	<--
US 2004176638	NCL	562/429.000; 568/028.000; 260/665.00R	
	ECLA	C07C255/58; C07C315/04; C07C317/14; C07C319/14; C07D301/20	<--
US 2005090682	NCL	558/410.000	<--

OS CASREACT 140:235504

AB **Racemic** N-[4-cyano-3-trifluoromethylphenyl]-3-[4-fluorophenylsulfonyl]-2-hydroxy-2-methylpropionamide (**bicalutamide**) was prepared starting from Et pyruvate and Me methacrylate. Thus, 5-amino-2-cyanobenzotrifluoride was treated with DABCO and reacted with deprotonated Et 2-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropionate (prepared from Et pyruvate) to give 40% **bicalutamide.** Micronized particles of **bicalutamide** can be obtained as pharmaceutical compns. that are useful for its anti-androgen activity (no data). **Bicalutamide** intermediates were also prepared, including Et 2-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropionate, Me 2,3-epoxy-2-methylpropionate and 2-hydroxy-2-methyl-3-(4-fluorophenylthio)propionic acid. The present invention further discloses the isolation and purification of **bicalutamide** by various **crystallization** methods.

ST **bicalutamide** prepn **crystn** micronization; cyanophenyl fluorophenylsulfonyl hydroxy propionamide prepn **crystn** micronization

IT Ligroine
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** solvent; preparation, micronization and **crystallization** of **bicalutamide**)

IT Drug delivery systems
(microparticles; preparation, micronization and **crystallization** of **bicalutamide**)

IT **Crystallization**
(preparation, micronization and **crystallization** of **bicalutamide**)

IT 60-29-7, Diethyl ether, uses 64-17-5, Ethanol, uses 67-56-1, Methanol,

uses 67-63-0, Isopropanol, uses 67-64-1, Acetone, uses 67-66-3, Chloroform, uses 67-68-5, DMSO, uses 68-12-2, DMF, uses 71-23-8, Propanol, uses 75-05-8, Acetonitrile, uses 75-09-2, Dichloromethane, uses 107-06-2, 1,2-Dichloroethane, uses 108-10-1, Isobutyl methyl ketone 108-88-3, Toluene, uses 109-99-9, THF, uses 110-54-3, Hexane, uses **141-78-6, Ethyl acetate**, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** solvent; preparation, micronization and **crystallization** of **bicalutamide**)

IT **90357-06-5P, Bicalutamide**
RL: **PEP (Physical, engineering or chemical process)**; **PUR (Purification or recovery)**; **PYP (Physical process)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**; **PROC (Process)**
(preparation, micronization and **crystallization** of **bicalutamide**)

IT 80-62-6, Methyl methacrylate 371-42-6, 4-Fluorothiophenol 455-15-2, 4-Fluorophenyl methyl sulfone 617-35-6, Ethyl pyruvate 654-70-6, 4-Cyano-3-(trifluoromethyl)aniline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation, micronization and **crystallization** of **bicalutamide**)

IT 58653-97-7P, Methyl 2-methyl-2-oxiranecarboxylate 339530-91-5P 478190-74-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, micronization and **crystallization** of **bicalutamide**)

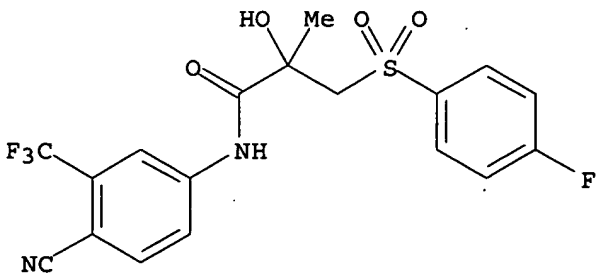
IT **141-78-6, Ethyl acetate**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** solvent; preparation, micronization and **crystallization** of **bicalutamide**)

RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)

Et—O—Ac

IT **90357-06-5P, Bicalutamide**
RL: **PEP (Physical, engineering or chemical process)**; **PUR (Purification or recovery)**; **PYP (Physical process)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**; **PROC (Process)**
(preparation, micronization and **crystallization** of **bicalutamide**)

RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



L79 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:80481** HCAPLUS

DN **140:133855**
ED Entered STN: 01 Feb 2004
TI Process for the preparation of **crystalline** nanoparticle dispersions
IN Skantze, Tommy Urban; Lindfors, Per Lennart; Forssen, Sara
PA Astrazeneca Ab, Swed.; Astrazeneca UK Limited
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-10
ICS A61K009-14; A61K009-51
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004009057	A1	20040129	WO 2003-GB3044	20030714 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2492709	AA	20040129	CA 2003-2492709	20030714 <--
EP 1524964	A1	20050427	EP 2003-738346	20030714 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI GB 2002-16700	A	20020718 <--		
WO 2003-GB3044	W	20030714		

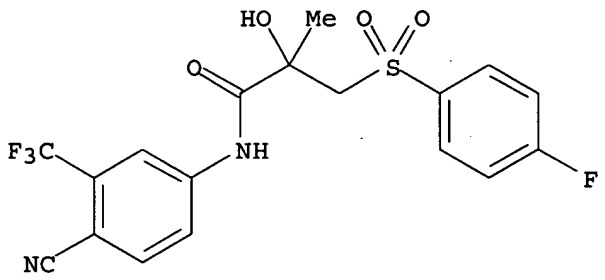
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004009057	ICM	A61K009-10
	ICS	A61K009-14; A61K009-51
WO 2004009057	ECLA	A61K009/51 <--

AB A process for the preparation of a dispersion of **crystalline** nanoparticles in an aqueous medium comprises combining (i) a first solution comprising a substantially water-insol. substance in a water-miscible organic solvent with; (ii) an aqueous phase comprising water and optionally a stabilizer, to form a dispersion of **amorphous** particles; and (iii) sonicating the dispersion of **amorphous** particles for a sufficient period to form **crystalline** nanoparticles of the substantially water-insol. substance. The process provides nano-**crystals** with a mean hydrodynamic diameter of <1 μm, particularly <300 nm and is particularly useful for the preparation of nano-**crystalline** dispersions of pharmaceutical substances. Thus, 0.010 mL of a solution of 100 mM felodipine in dimethylacetamide was added rapidly to 0.990 mL of an aqueous solution containing 0.2% polyvinylpyrrolidone and 0.25 mM sodium dodecyl sulfate under sonication for 30 min. The resulting particles were **crystalline** with a mean hydrodynamic diameter of 165 nm (no change in particle size was observed over 2 h).

ST **cryst** particle dispersion felodipine nanoparticle
IT Surfactants
(amphiphilic; process for preparation of **crystalline** nanoparticle dispersions)
IT Surfactants
(anionic; process for preparation of **crystalline** nanoparticle dispersions)

IT Drug delivery systems
(nanoparticles; process for preparation of **crystalline** nanoparticle dispersions)
IT Solvents
(organic; process for preparation of **crystalline** nanoparticle dispersions)
IT Dispersing agents
(polymeric; process for preparation of **crystalline** nanoparticle dispersions)
IT Particle size distribution
Stabilizing agents
(process for preparation of **crystalline** nanoparticle dispersions)
IT 151-21-3, Sodium dodecyl sulfate, biological studies 9003-39-8, Polyvinylpyrrolidone 72509-76-3, Felodipine **90357-06-5**, **Bicalutamide** 145040-37-5, Candesartan cilexetil 168273-06-1 288104-79-0 548759-96-2 650588-33-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(process for preparation of **crystalline** nanoparticle dispersions)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Doty, M; US 2003059472 A1 2003
(2) Magdassi, S; WO 9900113 A 1999 HCAPLUS
(3) Patrick, S; WO 9814174 A 1998 HCAPLUS
(4) Ruch, F; JOURNAL OF COLLOID AND INTERFACE SCIENCE 2000, V229(1), P207 HCAPLUS
(5) Sjoestroem, B; JOURNAL OF DISPERSION SCIENCE AND TECHNOLOGY 1994, V15(1), P89 HCAPLUS
(6) Sjostrom, B; JOURNAL OF PHARMACEUTICAL SCIENCES 1993, V82(6), P584 MEDLINE
IT **90357-06-5**, **Bicalutamide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(process for preparation of **crystalline** nanoparticle dispersions)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



L79 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:511288 HCAPLUS
DN 139:85122
ED Entered STN: 04 Jul 2003
TI Process for preparing **bicalutamide** and **crystals** thereof
IN Shintaku, Tetsuya; Katsura, Tadashi; Itaya, Nobushige
PA Sumika Fine Chemicals Co., Ltd., Japan
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM C07C315-02
ICS C07C315-06; C07C317-46; A61K031-277; A61P005-28; A61P043-00
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

Section cross-reference(s): 1, 75

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2003053920	A1	20030703	WO 2002-JP13058	20021213	<--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
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	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
	BR 2002014933	A	20041214	BR 2002-14933	20021213	<--
	US 2003191337	A1	20031009	US 2003-362410	20030224	<--
	US 6740770	B2	20040525			
	US 2004133031	A1	20040708	US 2003-740140	20031218	<--
PRAI	JP 2001-380686	A	20011213	<--		
	JP 2002-166213	A	20020606	<--		
	WO 2002-JP13058	W	20021213			
	US 2003-362410	A3	20030224			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2003053920	ICM	C07C315-02	
	ICS	C07C315-06; C07C317-46; A61K031-277; A61P005-28; A61P043-00	
EP 1462442	ECLA	C07C315/02; C07C315/06; C07C317/46	<--
US 2003191337	NCL	558/413.000; 558/414.000	<--
US 2004133031	NCL	558/413.000	<--

AB The invention relates to **crystals** of **bicalutamide** having a specific **crystal** form, and industrially practicable processes for the production of **bicalutamide** and **crystals** thereof; these processes are excellent in environmental friendliness and economical efficiency. **Bicalutamide** was prepared by epoxidn. of N-methacryloyl-4-cyano-3-trifluoromethylaniline, followed by reaction with 4-fluorothiophenol, and oxidation

ST **bicalutamide crystal** prepn; methacryloylcyanotrifluoromethylaniline epoxidn

IT Addition reaction
(addition reaction of fluorothiophenol with epoxide derivs.)

IT **Crystal structure**
(**crystal** structure of **bicalutamide crystals**)

IT **Crystallization**
(**crystallization** of **bicalutamide** from **Et acetate**)

IT Hydrocarbons, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** of **bicalutamide** from solvents)

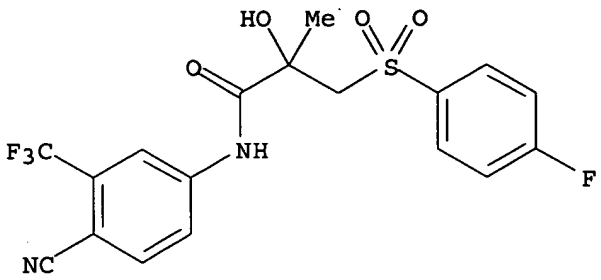
IT Epoxidation
(epoxidn. of methacryloylcyanotrifluoromethylaniline)

IT Oxidation
(oxidation of phenylthiopropionanilide derivs.)

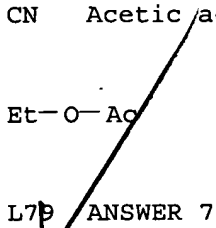
IT NMR (nuclear magnetic resonance)
(13C-NMR; NMR spectrum of **bicalutamide**)

IT 110-54-3, Hexane, uses 142-82-5, Heptane, uses
RL: NUU (Other use, unclassified); USES (Uses)

(**crystallization** of **bicalutamide** from solvents)
IT 316373-92-9P
RL: BYP (Byproduct); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **bicalutamide** in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of **crystals** of **bicalutamide**)
IT 1643-19-2, Tetrabutylammonium bromide
RL: CAT (Catalyst use); USES (Uses)
(preparation of **bicalutamide** in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of **crystals** of **bicalutamide**)
IT **90357-06-5P, Bicalutamide**
RL: **IMF (Industrial manufacture)**; PAC (Pharmacological activity); PRP (Properties); **PUR (Purification or recovery)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of **bicalutamide** in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of **crystals** of **bicalutamide**)
IT 2311-91-3P 90356-78-8P 90357-51-0P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **bicalutamide** in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of **crystals** of **bicalutamide**)
IT **141-78-6, Ethyl acetate**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of **bicalutamide** in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of **crystals** of **bicalutamide**)
IT 85-44-9, Phthalic anhydride 124-63-0, Methanesulfonyl chloride 371-42-6, 4-Fluorothiophenol 7722-84-1, Hydrogen peroxide, reactions 90357-53-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **bicalutamide** in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of **crystals** of **bicalutamide**)
IT 1571-33-1, Phenylphosphonic acid 11120-01-7, Sodium tungsten oxide 13472-45-2, Sodium tungstate
RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of **bicalutamide** in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of **crystals** of **bicalutamide**)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bristol-Myers Squibb Co; WO 0224638 A1 2002 HCAPLUS
(2) Bristol-Myers Squibb Co; US 200286902 A1 2002
(3) Richter Gedeon Vegyeszeti Gyar; WO 0100608 A1 2001 HCAPLUS
(4) Richter Gedeon Vegyeszeti Gyar; EP 1189898 A1 2001 HCAPLUS
(5) Tucker, H; Journal of Medicinal Chemistry 1988, V31(5), P954 HCAPLUS
IT **90357-06-5P, Bicalutamide**
RL: **IMF (Industrial manufacture)**; PAC (Pharmacological activity); PRP (Properties); **PUR (Purification or recovery)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of **bicalutamide** in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of **crystals** of **bicalutamide**)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



IT **141-78-6, Ethyl acetate**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of **bicalutamide** in multi-step process starting from N-methacryloyl-4-cyano-3-trifluoromethylaniline and process for production of **crystals** of **bicalutamide**)
RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)



L79 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:417600** HCAPLUS
DN **138:406952**
ED Entered STN: 01 Jun 2003
TI Pharmaceutical formulation comprising **bicalutamide**
IN Bateman, Nicola Frances; Cahill, Julie Kay; Carman, Neill Hugh; Cockshott, Ian Derek
PA Astrazeneca UK Limited, UK; Astrazeneca AB
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-16
ICS A61K031-56
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003043606	A1	20030530	WO 2002-GB5159	20021114 <--
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1448168	A1	20040825	EP 2002-779684	20021114 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	BR 2002014135	A	20041013	BR 2002-14135	20021114 <--
	US 2005038111	A1	20050217	US 2004-495012	20041004 <--
PRAI	SE 2001-3839	A	20011116 <--		
	WO 2002-GB5159	W	20021114		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003043606	ICM	A61K009-16
	ICS	A61K031-56
US 2005038111	NCL	514/522.000; 424/486.000
	ECLA	A61K009/00M18D; A61K031/56 <--

AB A composition comprising **bicalutamide** or a pharmaceutically acceptable salt or solvate thereof in a solid dispersion with an enteric polymer having a pKa of 3-6 is described. The composition further comprises an antiestrogen (e.g., tamoxifen citrate) and/or an aromatase inhibitor (e.g., anastrozole). An advantage of the composition is treating and/or preventing of at least one side effect selected from gynecomastia, breast tenderness, hot flushes, impotence and reduction in libido, while increasing the bioavailability of the drug, reducing inter-patient variability in plasma concns. of **bicalutamide**, enhancing the storage stability of the drug, and/or treating and/or reducing the risk of prostate cancer in a patient. For example, a solid dispersion of (R)-**bicalutamide** and hydroxypropyl Me cellulose phthalate (HP 55S) in a 1:3 ratio was prepared by spray drying showing enhanced drug release compared to a conventional tablet formulation.

ST **bicalutamide** enteric polymer solid dispersion; antiestrogen aromatase inhibitor **bicalutamide** solid dispersion

IT Estrogens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiestrogens, combination with; preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

IT Drug delivery systems
(capsules; preparation and therapeutic uses of **bicalutamide** -enteric polymer solid dispersions for capsules)

IT Menopause
(disorder, hot flash; preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

IT Mammary gland, disease
(gynecomastia; preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

IT Sexual behavior
(impotence; preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

IT Drug bioavailability
(increase of; preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

IT Prostate gland, neoplasm
(preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

IT Dissolution
(preparation, drug release, and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

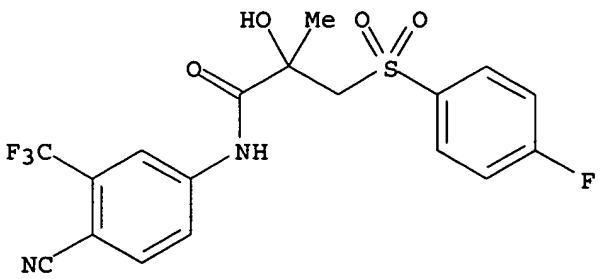
IT Drug delivery systems
(solid dispersions; preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

IT Drug interactions
(synergistic; preparation and therapeutic uses of solid dispersions containing **bicalutamide**, antiestrogen and/or aromatase inhibitor)

IT Mammary gland
(tenderness; preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

IT 10540-29-1, Tamoxifen 54965-24-1, Tamoxifen citrate 107868-30-4, Exemestane 112809-51-5, Letrozole 120511-73-1, Anastrozole
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination with; preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

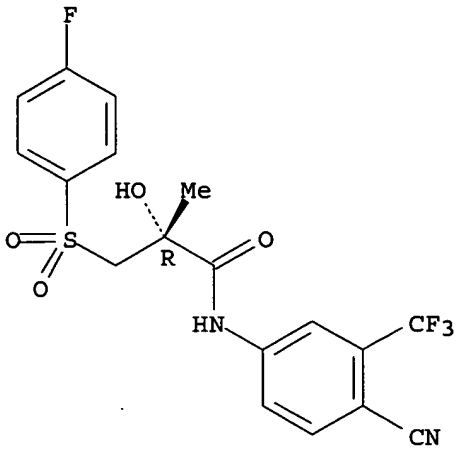
IT 9039-48-9, Aromatase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, combination with; preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)
IT **90357-06-5, Bicalutamide 113299-40-4**, (R)-**Bicalutamide**
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)
IT **9004-38-0**, Cellulose acetate phthalate **9050-31-1**, Hydroxypropyl methyl cellulose phthalate 25086-15-1, Eudragit L 100 **39340-12-0**, Hydroxypropyl methyl cellulose trimellitate **52907-01-4**, Cellulose acetate trimellitate 53237-50-6 **54391-89-8**, Cellulose acetate terephthalate **58858-21-2**, Hydroxypropyl methyl cellulose acetate **61811-44-7**, Hydroxypropyl methyl cellulose acetate phthalate **71138-97-1**, Hydroxypropyl methyl cellulose acetate succinate **89233-51-2**, Cellulose propionate phthalate **93792-59-7**, Hydroxypropyl methyl cellulose succinate **167077-74-9**, Cellulose propionate trimellitate **167077-75-0**, Cellulose butyrate trimellitate **188979-58-0**, Hydroxypropyl cellulose acetate phthalate **288141-80-0**, Methylcellulose acetate phthalate **288156-14-9**, Hydroxypropyl methyl cellulose acetate trimellitate **288307-50-6**, Hydroxypropyl cellulose butyrate phthalate **288307-51-7**, Cellulose acetate isophthalate **288372-69-0**, Ethylcellulose acetate phthalate **288372-70-3**, Hydroxypropyl cellulose acetate phthalate succinate **288372-71-4**, Methylcellulose acetate trimellitate **288372-72-5**, Ethylcellulose acetate trimellitate **288372-73-6**, Hydroxypropyl cellulose acetate trimellitate **288372-74-7**, Hydroxypropyl cellulose acetate trimellitate succinate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Denis, L; UROLOGY 1996, V47(SUPPL 1A), P26
IT **90357-06-5, Bicalutamide 113299-40-4**, (R)-**Bicalutamide**
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-

fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **9004-38-0**, Cellulose acetate phthalate **9050-31-1**, Hydroxypropyl methyl cellulose phthalate **39340-12-0**, Hydroxypropyl methyl cellulose trimellitate **52907-01-4**, Cellulose acetate trimellitate **54391-89-8**, Cellulose acetate terephthalate **58858-21-2**, Hydroxypropyl methyl cellulose acetate **61811-44-7**, Hydroxypropyl methyl cellulose acetate phthalate **71138-97-1**, Hydroxypropyl methyl cellulose acetate succinate **89233-51-2**, Cellulose propionate phthalate **93792-59-7**, Hydroxypropyl methyl cellulose succinate **167077-74-9**, Cellulose propionate trimellitate **167077-75-0**, Cellulose butyrate trimellitate **188979-58-0**, Hydroxypropyl cellulose acetate phthalate **288141-80-0**, Methylcellulose acetate phthalate **288156-14-9**, Hydroxypropyl methyl cellulose acetate trimellitate **288307-50-6**, Hydroxypropyl cellulose butyrate phthalate **288307-51-7**, Cellulose acetate isophthalate **288372-69-0**, Ethylcellulose acetate phthalate **288372-70-3**, Hydroxypropyl cellulose acetate phthalate succinate **288372-71-4**, Methylcellulose acetate trimellitate **288372-72-5**, Ethylcellulose acetate trimellitate **288372-73-6**, Hydroxypropyl cellulose acetate trimellitate **288372-74-7**, Hydroxypropyl cellulose acetate trimellitate succinate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and therapeutic uses of **bicalutamide** from solid dispersions with enteric polymers)

RN 9004-38-0 HCAPLUS

CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate (9CI) (CA INDEX NAME)

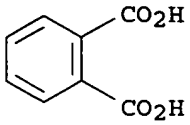
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

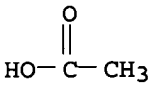
CM 2

CRN 88-99-3
CMF C8 H6 O4



CM 3

CRN 64-19-7
CMF C2 H4 O2



RN 9050-31-1 HCAPLUS
CN Cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

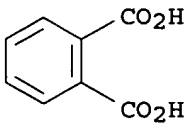
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

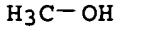
CM 2

CRN 88-99-3
CMF C8 H6 O4



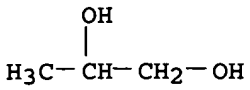
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 39340-12-0 HCAPLUS
CN Cellulose, 1,2,4-benzenetricarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

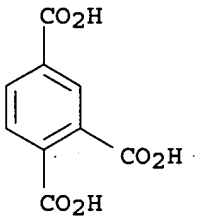
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 528-44-9
CMF C9 H6 O6



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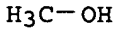
CRN 67-56-1
CMF C H4 O



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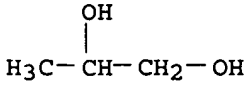
CMF C3 H8 O2



RN 52907-01-4 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)

CM 1

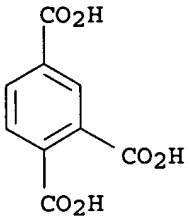
CRN 9004-34-6
CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

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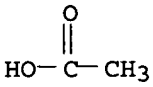
CMF C2 H4 O2



RN 54391-89-8 HCAPLUS
CN Cellulose, acetate hydrogen 1,4-benzenedicarboxylate (9CI) (CA INDEX NAME)

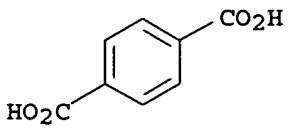
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-21-0
CMF C8 H6 O4



CM 3

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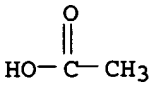
CMF C2 H4 O2



RN 58858-21-2 HCAPLUS
CN Cellulose, acetate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

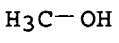
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

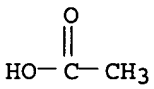
CM 2

CRN 67-56-1
CMF C H4 O



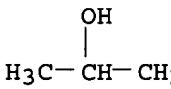
CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 61811-44-7 HCAPLUS
CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

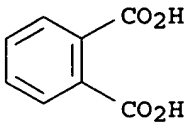
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

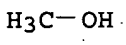
CM 2

CRN 88-99-3
CMF C8 H6 O4



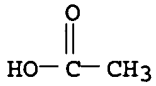
CM 3

CRN 67-56-1
CMF C H4 O



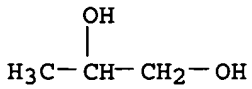
CM 4

CRN 64-19-7
CMF C2 H4 O2



CM 5

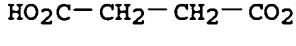
CRN 57-55-6
CMF C3 H8 O2



RN 71138-97-1 HCAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate (9CI) (CA INDEX NAME)

CM 1

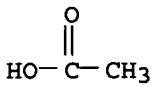
CRN 110-15-6
CMF C4 H6 O4



CM 2

CRN 64-19-7

CMF C2 H4 O2



CM 3

CRN 9004-65-3
CMF C3 H8 O2 . x C H4 O . x Unspecified

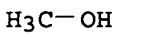
CM 4

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

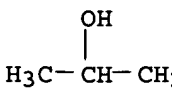
CM 5

CRN 67-56-1
CMF C H4 O



CM 6

CRN 57-55-6
CMF C3 H8 O2



RN 89233-51-2 HCAPLUS
CN Cellulose, hydrogen 1,2-benzenedicarboxylate propanoate (9CI) (CA INDEX NAME)

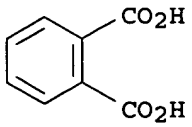
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

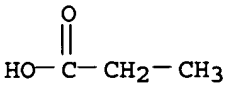
CM 2

CRN 88-99-3
CMF C8 H6 O4



CM 3

CRN 79-09-4
CMF C3 H6 O2



RN 93792-59-7 HCAPLUS
CN Cellulose, butanedioate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

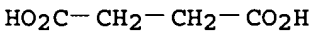
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

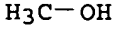
CM 2

CRN 110-15-6
CMF C4 H6 O4



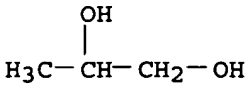
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 167077-74-9 HCAPLUS
CN Cellulose, dihydrogen 1,2,4-benzenetricarboxylate propanoate (9CI) (CA INDEX NAME)

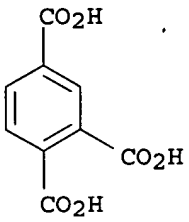
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

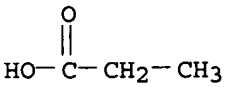
CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

CRN 79-09-4
CMF C3 H6 O2



RN 167077-75-0 HCAPLUS
CN Cellulose, butanoate dihydrogen 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)

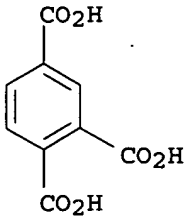
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

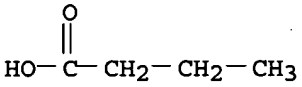
CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

CRN 107-92-6
CMF C4 H8 O2



RN 188979-58-0 HCAPLUS
CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

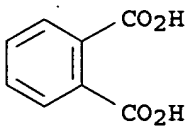
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

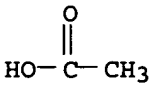
CM 2

CRN 88-99-3
CMF C8 H6 O4



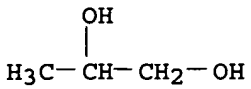
CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 288141-80-0 HCAPLUS
CN Cellulose, acetate 1,2-benzenedicarboxylate, methyl ether (9CI) (CA INDEX NAME)

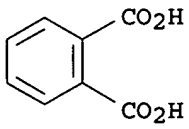
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

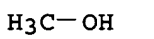
CM 2

CRN 88-99-3
CMF C8 H6 O4



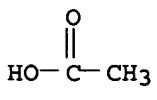
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 64-19-7
CMF C2 H4 O2

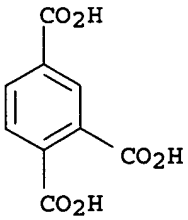


RN 288156-14-9 HCAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether, acetate 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)

CM 1

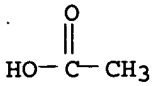
CRN 528-44-9

CMF C9 H6 O6



CM 2

CRN 64-19-7
CMF C2 H4 O2



CM 3

CRN 9004-65-3
CMF C3 H8 O2 . x C H4 O . x Unspecified

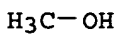
CM 4

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

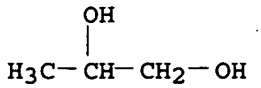
CM 5

CRN 67-56-1
CMF C H4 O



CM 6

CRN 57-55-6
CMF C3 H8 O2



RN 288307-50-6 HCAPLUS
CN Cellulose, 1,2-benzenedicarboxylate butanoate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

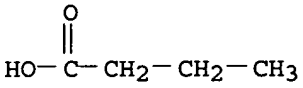
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

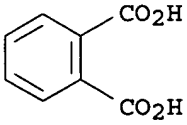
CM 2

CRN 107-92-6
CMF C4 H8 O2



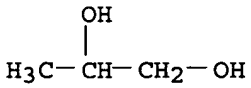
CM 3

CRN 88-99-3
CMF C8 H6 O4



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 288307-51-7 HCAPLUS
CN Cellulose, acetate 1,3-benzenedicarboxylate (9CI) (CA INDEX NAME)

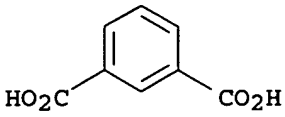
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

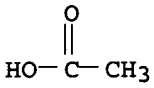
CM 2

CRN 121-91-5
CMF C8 H6 O4



CM 3

CRN 64-19-7
CMF C2 H4 O2



RN 288372-69-0 HCAPLUS
CN Cellulose, acetate 1,2-benzenedicarboxylate, ethyl ether (9CI) (CA INDEX NAME)

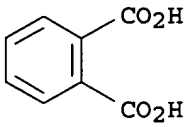
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

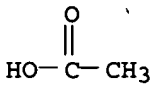
CM 2

CRN 88-99-3
CMF C8 H6 O4



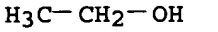
CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 64-17-5
CMF C2 H6 O



RN 288372-70-3 HCAPLUS
CN Cellulose, acetate 1,2-benzenedicarboxylate butanedioate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

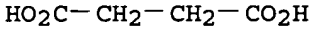
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

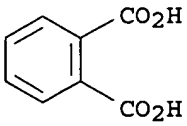
CM 2

CRN 110-15-6
CMF C4 H6 O4



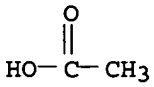
CM 3

CRN 88-99-3
CMF C8 H6 O4



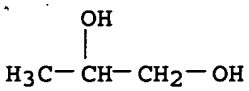
CM 4

CRN 64-19-7
CMF C2 H4 O2



CM 5

CRN 57-55-6
CMF C3 H8 O2



RN 288372-71-4 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate, methyl ether (9CI) (CA INDEX NAME)

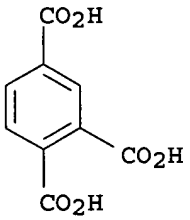
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

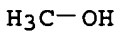
CM 2

CRN 528-44-9
CMF C9 H6 O6



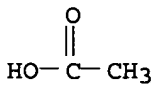
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 64-19-7
CMF C2 H4 O2



RN 288372-72-5 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate, ethyl ether (9CI) (CA INDEX NAME)

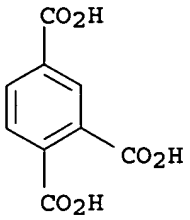
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

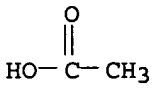
CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 64-17-5
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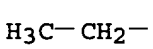


RN 288372-73-6 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

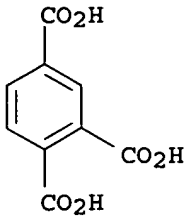
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 528-44-9
CMF C9 H6 O6



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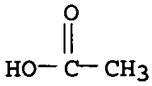

CM 4

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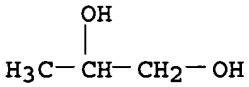


RN 288372-74-7 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate butanedioate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

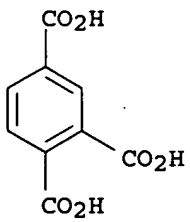
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 528-44-9
CMF C9 H6 O6



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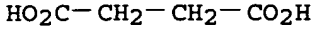

CM 4

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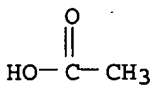

CM 5

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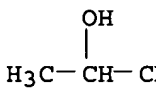

L79 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:319681** HCAPLUS
DN **138:343868**
ED Entered STN: 25 Apr 2003
TI Pharmaceutical formulation comprising (R)-**bicalutamide**
IN Bateman, Nicola Frances
PA Astrazeneca AB, Swed.; Astrazeneca UK Limited; Cahill, Julie Kay
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-14
ICS A61K031-275; A61P035-00
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003032950	A1	20030424	WO 2002-GB4621	20021011 <--

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JP 2004521963	T2	20040722	JP 2003-535754	20021011	<--
JP 3639587	B2	20050420			
EP 1439823	A1	20040728	EP 2002-770069	20021011	<--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRAI SE 2001-3424	A	20011015	<--
WO 2002-GB4621	W	20021011	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2003032950	ICM	A61K009-14	
	ICS	A61K031-275; A61P035-00	
WO 2003032950	ECLA	A61K009/14H6	<--
JP 2004521963	FTERM	4C076/AA36; 4C076/BB01; 4C076/CC27; 4C076/EE11; 4C076/EE24; 4C076/EE33; 4C076/FF25; 4C076/FF34; 4C076/FF63; 4C206/AA02; 4C206/JA35; 4C206/MA02; 4C206/MA05; 4C206/MA28; 4C206/MA29; 4C206/MA54; 4C206/MA72; 4C206/NA03; 4C206/NA11; 4C206/NA13; 4C206/ZB26	<--

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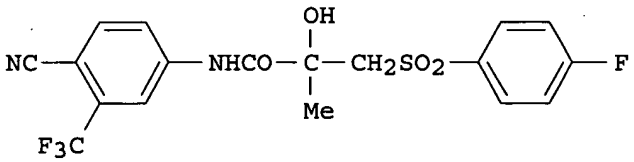


I

AB The present invention relates to a pharmaceutical formulation comprising (R)-**bicalutamide** (I) in a solid dispersion with an enteric polymer having a pKa from 3 to 6, wherein > 50 % of the drug is provided in the form of the R-enantiomer. The invention also relates to a daily pharmaceutical dose of the drug provided by such a formulation. In addition, the invention relates to the use of an enteric polymer having a pKa from 3 to 6 in solid dispersion with the drug, wherein > 50 % of the drug is provided in the form of the R-enantiomer, for increasing the bioavailability of the drug; for reducing inter-patient variability in plasma concns. of the drug; for enhancing the storage stability of the drug; or for treating and/or reducing the risk of prostate cancer in a patient. Solid dispersions of (R)-I were prepared with HP 55S, Eudragit L 100, and Aqoat LG.

ST **bicalutamide** pharmaceutical solid dispersion

IT Dissolution
(pharmaceutical formulation comprising (R)-**bicalutamide**)

IT Drug delivery systems
(solid dispersions; pharmaceutical formulation comprising (R)-**bicalutamide**)

IT **9050-31-1**, Hydroxypropyl methyl cellulose phthalate
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HP 55S; pharmaceutical formulation comprising (R)-**bicalutamide**)

IT **9004-38-0**, Cellulose acetate phthalate 25086-15-1, Eudragit L 100 **39340-12-0**, Hydroxypropyl methyl cellulose trimellitate **52907-01-4**, Cellulose acetate trimellitate 53237-50-6 **54391-89-8**, Cellulose acetate terephthalate **58858-21-2**, Hydroxypropyl methyl cellulose acetate **61811-44-7**, Hydroxypropyl methyl cellulose acetate phthalate **71138-97-1**, Hydroxypropyl

methyl cellulose acetate succinate **89233-51-2**, Cellulose propionate phthalate **93792-59-7**, Hydroxypropyl methyl cellulose succinate **167077-74-9**, Cellulose propionate trimellitate **167077-75-0**, Cellulose butyrate trimellitate **188979-58-0**, Hydroxypropyl cellulose acetate phthalate **288141-80-0**, Methyl cellulose acetate phthalate **288156-14-9**, Hydroxypropyl methyl cellulose acetate trimellitate **288307-50-6**, Hydroxypropyl cellulose butyrate phthalate **288307-51-7**, Cellulose acetate isophthalate **288372-69-0**, Ethyl cellulose acetate phthalate **288372-70-3**, Hydroxypropylcellulose acetate phthalate succinate **288372-71-4**, Methyl cellulose acetate trimellitate **288372-72-5**, Ethyl cellulose acetate trimellitate **288372-73-6**, Hydroxypropyl cellulose acetate trimellitate **288372-74-7**, Hydroxypropyl cellulose acetate succinate trimellitate
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation comprising (R)-**bicalutamide**)

IT **90357-06-5**, **Bicalutamide 113299-40-4**, Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (R)-
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation comprising (R)-**bicalutamide**)

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Bateman, N; WO 02067893 A 2002 HCAPLUS
(2) Cockshott, I; BRITISH JOURNAL OF CLINICAL PHARMACOLOGY 1993, V36(4), P339 HCAPLUS
(3) Kay, C; WO 02080902 A 2002 HCAPLUS
(4) McKillop, D; XENOBIOTICA 1993, V23(11), P1241 HCAPLUS
(5) McKillop, D; XENOBIOTICA 1995, V25(6), P623 HCAPLUS
(6) Sepracor Inc; WO 9519770 A 1995 HCAPLUS

IT **9050-31-1**, Hydroxypropyl methyl cellulose phthalate
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HP 55S; pharmaceutical formulation comprising (R)-**bicalutamide**)

RN 9050-31-1 HCAPLUS

CN Cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

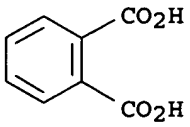
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

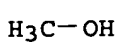
CM 2

CRN 88-99-3
CMF C8 H6 O4



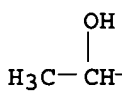
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 57-55-6
CMF C3 H8 O2



IT **9004-38-0**, Cellulose acetate phthalate **39340-12-0**, Hydroxypropyl methyl cellulose trimellitate **52907-01-4**, Cellulose acetate trimellitate **54391-89-8**, Cellulose acetate terephthalate **58858-21-2**, Hydroxypropyl methyl cellulose acetate **61811-44-7**, Hydroxypropyl methyl cellulose acetate phthalate **71138-97-1**, Hydroxypropyl methyl cellulose acetate succinate **89233-51-2**, Cellulose propionate phthalate **93792-59-7**, Hydroxypropyl methyl cellulose succinate **167077-74-9**, Cellulose propionate trimellitate **167077-75-0**, Cellulose butyrate trimellitate **188979-58-0**, Hydroxypropyl cellulose acetate phthalate **288141-80-0**, Methyl cellulose acetate phthalate **288156-14-9**, Hydroxypropyl methyl cellulose acetate trimellitate **288307-50-6**, Hydroxypropyl cellulose butyrate phthalate **288307-51-7**, Cellulose acetate isophthalate **288372-69-0**, Ethyl cellulose acetate phthalate **288372-70-3**, Hydroxypropylcellulose acetate phthalate succinate **288372-71-4**, Methyl cellulose acetate trimellitate **288372-72-5**, Ethyl cellulose acetate trimellitate **288372-73-6**, Hydroxypropyl cellulose acetate trimellitate **288372-74-7**, Hydroxypropyl cellulose acetate succinate trimellitate
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation comprising (R)-**bicalutamide**)

RN 9004-38-0 HCAPLUS
CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate (9CI) (CA INDEX NAME)

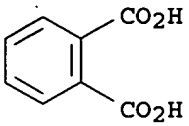
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

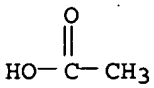
CM 2

CRN 88-99-3
CMF C8 H6 O4



CM 3

CRN 64-19-7
CMF C2 H4 O2



RN 39340-12-0 HCAPLUS
CN Cellulose, 1,2,4-benzenetricarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

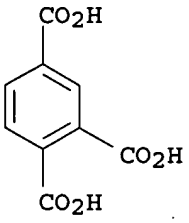
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 528-44-9
CMF C9 H6 O6



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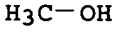

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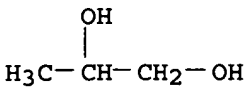


RN 52907-01-4 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)

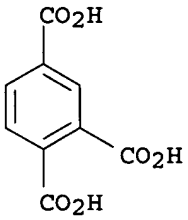
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

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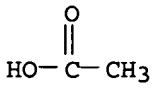


RN 54391-89-8 HCAPLUS
CN Cellulose, acetate hydrogen 1,4-benzenedicarboxylate (9CI) (CA INDEX NAME)

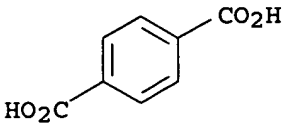
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

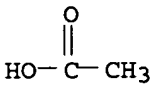
CM 2

CRN 100-21-0
CMF C8 H6 O4



CM 3

CRN 64-19-7
CMF C2 H4 O2



RN 58858-21-2 HCAPLUS
CN Cellulose, acetate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

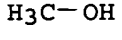
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 67-56-1
CMF C H4 O



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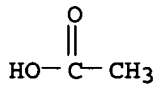
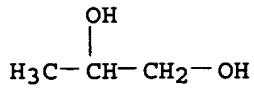


CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 61811-44-7 HCAPLUS
CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

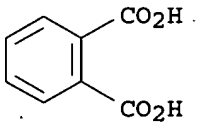
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 88-99-3
CMF C8 H6 O4



CM 3

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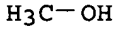

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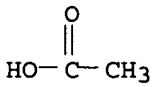

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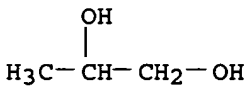
CMF C3 H8 O2



RN 71138-97-1 HCAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate (9CI) (CA INDEX NAME)

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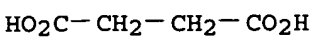
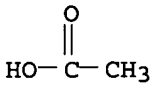


CM 2

CRN 64-19-7
CMF C2 H4 O2



CM 3

CRN 9004-65-3
CMF C3 H8 O2 . x C H4 O . x Unspecified

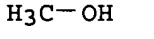
CM 4

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

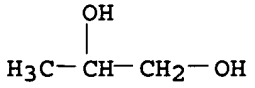
CM 5

CRN 67-56-1
CMF C H4 O



CM 6

CRN 57-55-6
CMF C3 H8 O2



RN 89233-51-2 HCAPLUS
CN Cellulose, hydrogen 1,2-benzenedicarboxylate propanoate (9CI) (CA INDEX NAME)

CM 1

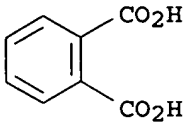
CRN 9004-34-6

CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

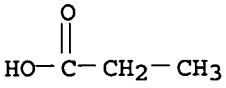
CM 2

CRN 88-99-3
CMF C8 H6 O4



CM 3

CRN 79-09-4
CMF C3 H6 O2



RN 93792-59-7 HCAPLUS
CN Cellulose, butanedioate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

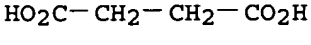
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

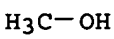
CM 2

CRN 110-15-6
CMF C4 H6 O4



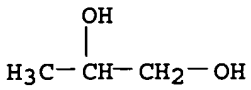
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 167077-74-9 HCAPLUS
CN Cellulose, dihydrogen 1,2,4-benzenetricarboxylate propanoate (9CI) (CA INDEX NAME)

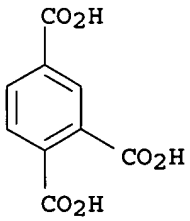
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

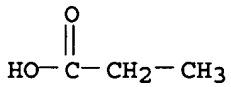
CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

CRN 79-09-4
CMF C3 H6 O2



RN 167077-75-0 HCAPLUS
CN Cellulose, butanoate dihydrogen 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)

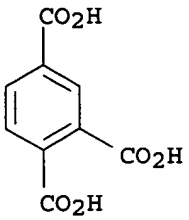
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

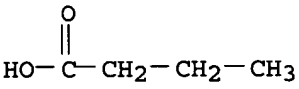
CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

CRN 107-92-6
CMF C4 H8 O2



RN 188979-58-0 HCAPLUS
CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

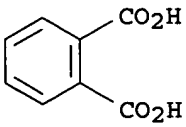
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

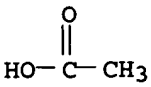
CM 2

CRN 88-99-3
CMF C8 H6 O4



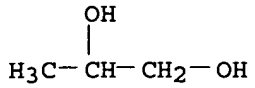
CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 288141-80-0 HCAPLUS
CN Cellulose, acetate 1,2-benzenedicarboxylate, methyl ether (9CI) (CA INDEX NAME)

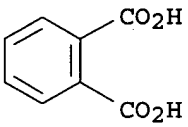
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

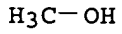
CM 2

CRN 88-99-3
CMF C8 H6 O4



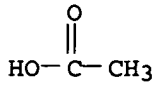
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

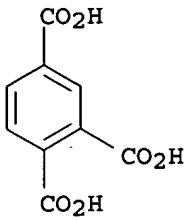
CRN 64-19-7
CMF C2 H4 O2



RN 288156-14-9 HCAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether, acetate 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)

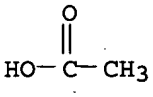
CM 1

CRN 528-44-9
CMF C9 H6 O6



CM 2

CRN 64-19-7
CMF C2 H4 O2



CM 3

CRN 9004-65-3
CMF C3 H8 O2 . x C H4 O . x Unspecified

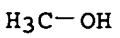
CM 4

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

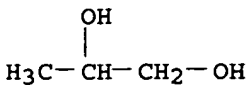
CM 5

CRN 67-56-1
CMF C H4 O



CM 6

CRN 57-55-6
CMF C3 H8 O2



RN 288307-50-6 HCAPLUS
CN Cellulose, 1,2-benzenedicarboxylate butanoate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

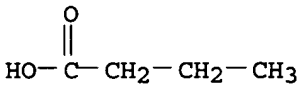
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

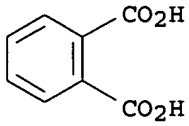
CM 2

CRN 107-92-6
CMF C4 H8 O2



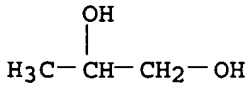
CM 3

CRN 88-99-3
CMF C8 H6 O4



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 288307-51-7 HCAPLUS
CN Cellulose, acetate 1,3-benzenedicarboxylate (9CI) (CA INDEX NAME)

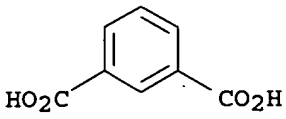
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

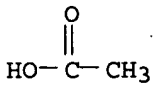
CM 2

CRN 121-91-5
CMF C8 H6 O4



CM 3

CRN 64-19-7
CMF C2 H4 O2



RN 288372-69-0 HCAPLUS
CN Cellulose, acetate 1,2-benzenedicarboxylate, ethyl ether (9CI) (CA INDEX NAME)

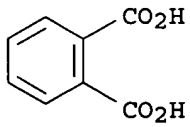
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

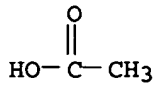
CM 2

CRN 88-99-3
CMF C8 H6 O4



CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 64-17-5

CMF C2 H6 O

H_3C-CH_2-OH

RN 288372-70-3 HCAPLUS
CN Cellulose, acetate 1,2-benzenedicarboxylate butanedioate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

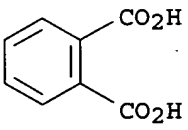
CM 2

CRN 110-15-6
CMF C4 H6 O4

$HO_2C-CH_2-CH_2-CO_2H$

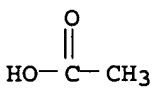
CM 3

CRN 88-99-3
CMF C8 H6 O4



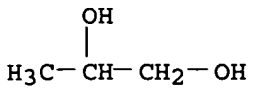
CM 4

CRN 64-19-7
CMF C2 H4 O2



CM 5

CRN 57-55-6
CMF C3 H8 O2



RN 288372-71-4 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate, methyl ether (9CI) (CA INDEX NAME)

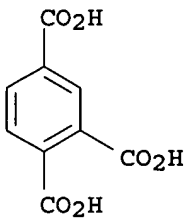
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

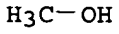
CM 2

CRN 528-44-9
CMF C9 H6 O6



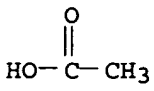
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 64-19-7
CMF C2 H4 O2



RN 288372-72-5 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate, ethyl ether (9CI) (CA INDEX NAME)

CM 1

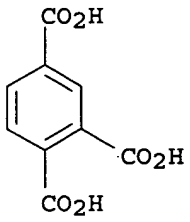
CRN 9004-34-6

CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

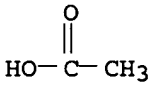
CM 2

CRN 528-44-9
CMF C9 H6 O6



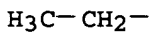
CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 64-17-5
CMF C2 H6 O



RN 288372-73-6 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

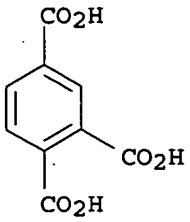
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

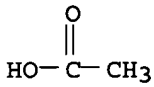
CM 2

CRN 528-44-9
CMF C9 H6 O6



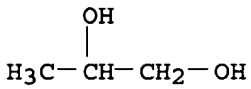
CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 288372-74-7 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate butanedioate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

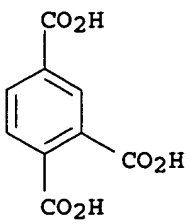
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

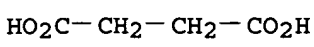
CM 2

CRN 528-44-9
CMF C9 H6 O6



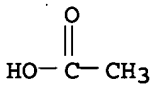
CM 3

CRN 110-15-6
CMF C4 H6 O4



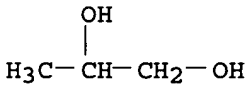
CM 4

CRN 64-19-7
CMF C2 H4 O2

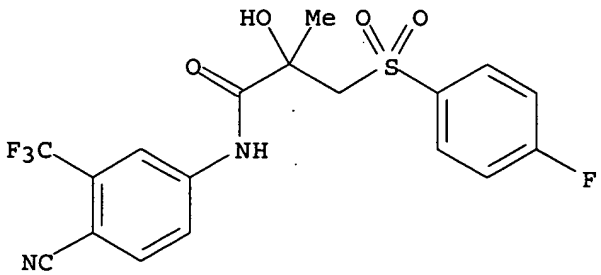


CM 5

CRN 57-55-6
CMF C3 H8 O2

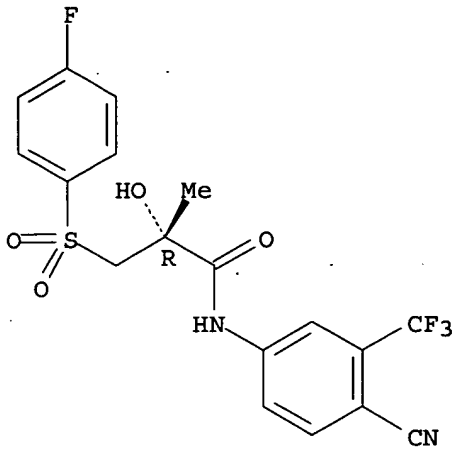


IT **90357-06-5, Bicalutamide 113299-40-4,**
Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (R)-
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation comprising (R)-**bicalutamide**)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



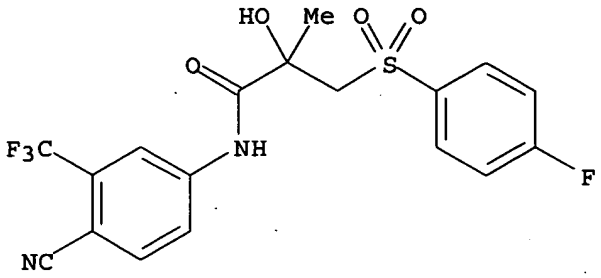
L79 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:300625 HCAPLUS
DN 138:321017
ED Entered STN: 18 Apr 2003
TI Process for making **bicalutamide** using a p-fluorobenzenesulfinic acid salt.
IN Thijs, Lambertus; Keltjens, Rolf; Ettema, Gerrit Jan Bouke
PA **Synthon B.V., Neth.**
SO U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-277
ICS C07C317-32
INCL 514522000; 558413000
CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003073742	A1	20030417	US 2002-261492	20021002
US 6818766	B2	20041116		
WO 2004031136	A1	20040415	WO 2003-EP11166	20031001
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004068135	A1	20040408	US 2003-682530	20031010
PRAI US 2002-261492	A	20021002		

CLASS

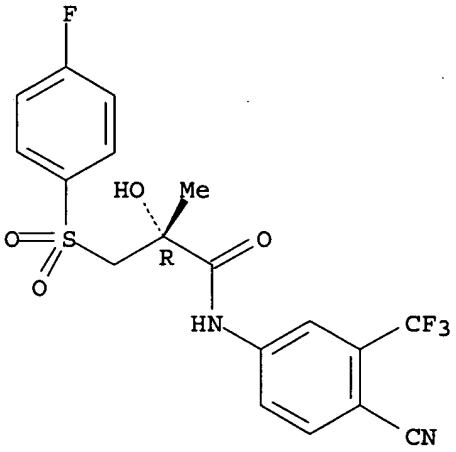
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2003073742	ICM	A61K031-277
	ICS	C07C317-32
	INCL	514522000; 558413000
US 2003073742	NCL	544/105.000; 548/227.000; 549/296.000; 558/413.000; 558/414.000; 560/011.000; 562/429.000
	ECLA	C07C315/00; C07C317/46
US 2004068135	NCL	558/413.000

ECLA C07C315/00; C07C317/46
OS CASREACT 138:321017; MARPAT 138:321017
AB Title process is claimed. Thus, N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-oxiranecarboxamide (preparation given), Na p-fluorobenzenesulfinate, and Bu4NBr were refluxed together for 96 h to give 48% **bicalutamide**.
ST **bicalutamide** prepn; cyanotrifluoromethylphenylmethyloxiranecarboxamide fluorobenzenesulfinate reaction
IT **90357-06-5P, Bicalutamide 113299-40-4P**
RL: **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**
(process for making **bicalutamide** using a p-fluorobenzenesulfinic acid salt)
IT 77-76-9, 2,2-Dimethoxypropane 80-62-6, Methyl methacrylate 369-51-7D, p-Fluorobenzenesulfinic acid, salts 654-70-6, 4-Cyano-3-trifluoromethylaniline 824-80-6, Sodium p-fluorobenzenesulfinate 920-46-7, Methacryloyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for making **bicalutamide** using a p-fluorobenzenesulfinic acid salt)
IT 2231-91-6P 19860-56-1P, Methyl 2,3-dihydroxy-2-methylpropionate 58653-97-7P 90357-51-0P 90357-53-2P 216665-20-2P 216665-25-7P 316373-92-9P 316373-93-0P 316373-94-1P 316373-95-2P 316373-97-4P 316373-98-5P 512776-88-4P 512776-89-5P 512776-90-8P 512776-91-9P 512776-92-0P 512776-93-1P 512776-94-2P 512776-95-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for making **bicalutamide** using a p-fluorobenzenesulfinic acid salt)
IT 2216-51-5 39637-74-6, (-)-Camphanic acid chloride
RL: RGT (Reagent); RACT (Reactant or reagent)
(process for making **bicalutamide** using a p-fluorobenzenesulfinic acid salt)
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anon; EP 0100172 1987 HCAPLUS
(2) Anon; WO 0058279 2000 HCAPLUS
(3) Anon; WO 0100608 A1 2001 HCAPLUS
(4) Anon; WO 0128990 A2 2001 HCAPLUS
(5) Anon; WO 0134563 A1 2001 HCAPLUS
(6) Anon; WO 02100339 A2 2002 HCAPLUS
(7) Gao; J. Am. Chem. Soc 1987, P5765 HCAPLUS
(8) Gray; US 5985868 A 1999 HCAPLUS
(9) Johnson; Catalytic Asymmetric Dihydroxylation 1993, P227 HCAPLUS
(10) Johnson; Catalytic Asymmetric Epoxidation of Allylic Alcohols 1993, P103
(11) Maryanoff; J. Med. Chem. 1987, V30, P880 HCAPLUS
(12) Miller; US 6019957 A 2000 HCAPLUS
(13) Oxley; Journal of The Chemical Society 1946, P763 HCAPLUS
(14) Shao; J. Org. Chem. 1995, V60, P790 HCAPLUS
(15) Takahashi; US 6300514 B1 2001 HCAPLUS
(16) Tucker; US 4636505 A 1987 HCAPLUS
(17) Tucker; J. Med. Chem. 1988, V31, P954 HCAPLUS
(18) Zefirov; Journal of Organic Chemistry of the USSR 1986, V22(2), P398
IT **90357-06-5P, Bicalutamide 113299-40-4P**
RL: **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**
(process for making **bicalutamide** using a p-fluorobenzenesulfinic acid salt)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L79 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:964133** HCAPLUS
DN **138:24551**
ED Entered STN: 20 Dec 2002
TI Preparation of rac-**bicalutamide**
IN Dolitzky, Ben-Zion; Reany, Ofer; Shamai, Jenny
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.; Biogal Gyogyszergyar
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 63
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002100339	A2	20021219	WO 2002-US18329	20020613 <--
WO 2002100339	A3	20031016		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

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            UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
            KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
            GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
            GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2448571          AA    20021219    CA 2002-2448571        20020613 <--
     EP 1406855          A2    20040414    EP 2002-739801         20020613 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     US 2005090682       A1    20050428    US 2004-994267         20041123 <--
PRAI US 2001-298009P     P     20010613  <--
     US 2002-371069P     P     20020409  <--
     US 2002-170721      A3    20020613  <--
     WO 2002-US18329     W     20020613  <--
     US 2004-791468      A3    20040301
     US 2004-796313      A3    20040308
     US 2004-796822      A3    20040308
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 WO 2002100339    ICM    A61K
 WO 2002100339    ECLA   C07C255/58; C07C315/04; C07C317/14; C07C319/14;
                         C07D301/20                                      <--
 US 2005090682    NCL    558/410.000                                     <--
OS   CASREACT 138:24551
AB   Racemic and optically active N-[4-cyano-3-trifluoromethylphenyl]-
     3-[4-fluorophenylsulfonyl]-2-hydroxy-2-Me propionamide (
     bicalutamide) were prepared starting from Et pyruvate and Me
     methacrylate. Thus, 5-amino-2-cyanobenzotrifluoride was treated with
     DABCO and reacted with deprotonated ethyl-[2-(4-fluorophenyl
     sulfone)]-2-hydroxy propionate (prepared from Et pyruvate) to give %40 rac-
     bicalutamide. Micronized particles of rac-bicalutamide
     can be obtained as pharmaceutical compns. that are useful for its
     anti-androgen activity (no data). Bicalutamide intermediates
     were also prepared, including ethyl-[2-(4-fluorophenyl sulfone)]-2-hydroxy
     propionate, 1,2-epoxy-2-Me propionate and 2-hydroxy-2-methyl-3-(4-
     fluorophenylthio) propionic acid.
ST   bicalutamide prepn; cyanotrifluoromethylphenylfluorophenylsulfon
     ylhydroxymethylpropionamide prepn
IT   280-57-9, DABCO
     RL: RGT (Reagent); RACT (Reactant or reagent)
        (anion stabilizer; preparation of rac-bicalutamide)
IT   109-72-8, Butyl lithium, reactions   1310-58-3, Potassium hydroxide,
     reactions   1310-73-2, Sodium hydroxide, reactions
     RL: RGT (Reagent); RACT (Reactant or reagent)
        (base; preparation of rac-bicalutamide)
IT   67-66-3, Chloroform, uses
     RL: NUU (Other use, unclassified); USES (Uses)
        (extraction with; preparation of rac-bicalutamide)
IT   7727-37-9, Nitrogen, uses
     RL: NUU (Other use, unclassified); USES (Uses)
        (inert atmospheric; preparation of rac-bicalutamide)
IT   478190-75-9   478190-76-0
     RL: FMU (Formation, unclassified); RCT (Reactant); FORM (Formation,
     nonpreparative); RACT (Reactant or reagent)
        (preparation of rac-bicalutamide)
IT   141-78-6, Ethyl acetate, uses
     RL: NUU (Other use, unclassified); USES (Uses)
        (preparation of rac-bicalutamide)
IT   80-62-6, Methyl methacrylate   371-42-6, 4-Fluorothiophenol   455-15-2,
     4-Fluorophenyl methyl sulfone   617-35-6, Ethyl pyruvate   654-70-6,
     4-Cyano-3-(trifluoromethyl)aniline   37222-66-5, Oxone
     RL: RCT (Reactant); RACT (Reactant or reagent)
```
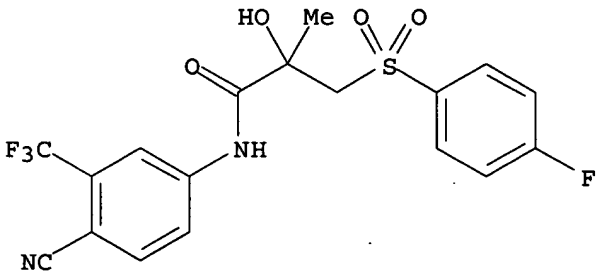

(preparation of rac-**bicalutamide**)
IT 58653-97-7P, Methyl 2-methyl-2-oxiranecarboxylate 339530-91-5P 478190-74-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of rac-**bicalutamide**)
IT 7647-01-0, Hydrochloric acid, reactions 7664-38-2, Phosphoric acid, reactions 7697-37-2, Nitric acid, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of rac-**bicalutamide**)
IT **90357-06-5P, Bicalutamide 113299-38-0P 113299-40-4P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of rac-**bicalutamide**)
IT 60-29-7, Diethyl ether, uses 67-56-1, Methanol, uses 109-99-9, THF, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; preparation of rac-**bicalutamide**)
IT **141-78-6, Ethyl acetate**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of rac-**bicalutamide**)
RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)

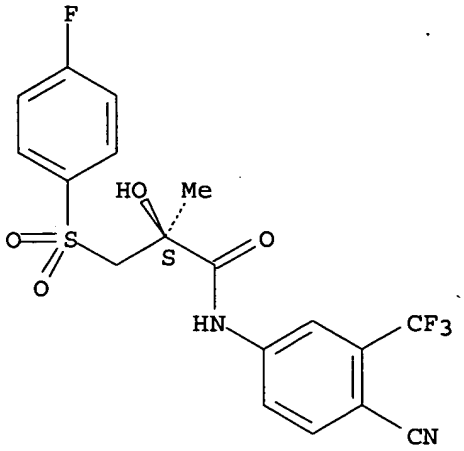
Et—O—Ac

IT **90357-06-5P, Bicalutamide 113299-38-0P 113299-40-4P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of rac-**bicalutamide**)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



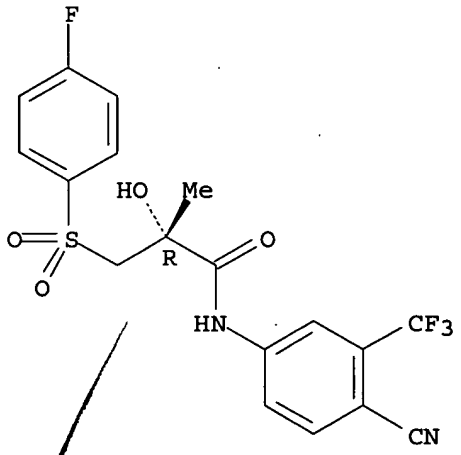
RN 113299-38-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L79 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:777696** HCAPLUS
DN **137:268489**
ED Entered STN: 11 Oct 2002
TI Process for producing fine granulate drug
IN Yanai, Shigeo; Saito, Kazuhiro; Hoshino, Tetsuo
PA Takeda Chemical Industries, Ltd., Japan
SO PCT Int. Appl., 156 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM A61K009-14
ICS A61K047-02; A61K047-12; A61K047-24; A61K047-34; A61K047-36; A61K047-38; A61K047-42; A61K031-38; A61K031-382; A61K031-4162
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002078673	A1	20021010	WO 2002-JP3049	20020328 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

JP 2002356419 A2 20021213 JP 2002-90881 20020328 <--
PRAI JP 2001-95914 A 20010329 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002078673	ICM	A61K009-14
	ICS	A61K047-02; A61K047-12; A61K047-24; A61K047-34; A61K047-36; A61K047-38; A61K047-42; A61K031-38; A61K031-382; A61K031-4162

AB A process is presented for producing a water-insol. or hardly water-soluble drug in the form of fine granules, which can be orally administered or injected, comprising quickly mixing an aqueous solvent with an aqueous solvent-miscible organic solvent solution containing a water-insol. or hardly water-soluble drug having been improved in the wettability with at least one of the solvents. The compds. for improving wettability are sugars, CM-cellulose, phospholipids, surfactants, amphoteric polymers, proteins, and inorg. salts.

ST granule drug delivery system

IT Carbohydrates, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(as wetting agents in producing fine granulate drug with solvents)

IT Phospholipids, uses
RL: NUU (Other use, unclassified); USES (Uses)
(as wetting agents in producing fine granulate drug with solvents)

IT Phosphatidylcholines, uses
RL: NUU (Other use, unclassified); USES (Uses)
(distearoyl; as wetting agents in producing fine granulate drug with solvents)

IT Drug delivery systems
(granules; process for producing fine granulate drug)

IT Solvents
(process for producing fine granulate drug with solvents)

IT **9004-32-4**, Carboxymethyl cellulose 106392-12-5, Ethylene oxide-propylene oxide block copolymer
RL: NUU (Other use, unclassified); USES (Uses)
(as wetting agents in producing fine granulate drug with solvents)

IT 302-22-7, Chlormadinone acetate 432-60-0, Allylestrenol 1253-28-7, Gestonorone caproate 13311-84-7, Flutamide 33765-68-3, Oxendolone 61536-83-2, Benzothiepin **90357-06-5**, **Bicalutamide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(wetting agents in producing fine granulate drug with solvents)

RE.CNT 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Fujisawa Pharmaceutical Co Ltd; JP 05155770 A 1992 HCAPLUS
(2) Fujisawa Pharmaceutical Co Ltd; IL 100011 A1 1992 HCAPLUS
(3) Fujisawa Pharmaceutical Co Ltd; CN 1061907 A 1992
(4) Fujisawa Pharmaceutical Co Ltd; CN 1069195 B 1992 HCAPLUS
(5) Fujisawa Pharmaceutical Co Ltd; CA 2054983 A 1992 HCAPLUS
(6) Fujisawa Pharmaceutical Co Ltd; ES 2061149 T3 1992 HCAPLUS
(7) Fujisawa Pharmaceutical Co Ltd; RU 2079304 C1 1992 HCAPLUS
(8) Fujisawa Pharmaceutical Co Ltd; HU 210760 B 1992 HCAPLUS
(9) Fujisawa Pharmaceutical Co Ltd; JP 2581359 B 1992 HCAPLUS
(10) Fujisawa Pharmaceutical Co Ltd; EP 484936 A1 1992 HCAPLUS
(11) Fujisawa Pharmaceutical Co Ltd; EP 484936 B1 1992 HCAPLUS

(12) Fujisawa Pharmaceutical Co Ltd; US 5368865 A 1992 HCAPLUS
(13) Fujisawa Pharmaceutical Co Ltd; US 5496564 A 1992 HCAPLUS
(14) Fujisawa Pharmaceutical Co Ltd; HU 60925 A2 1992 HCAPLUS
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(16) Fujisawa Pharmaceutical Co Ltd; ZA 9108846 A 1992 HCAPLUS
(17) Fujisawa Pharmaceutical Co Ltd; AU 9187099 A1 1992 HCAPLUS
(18) Fujisawa Pharmaceutical Co Ltd; JP 06183970 A 1994 HCAPLUS
(19) Fujisawa Pharmaceutical Co Ltd; JP 10505818 A 1996
(20) Fujisawa Pharmaceutical Co Ltd; ZA 9507201 A 1996 HCAPLUS
(21) Fujisawa Pharmaceutical Co Ltd; AU 9532658 A1 1996 HCAPLUS
(22) Fujisawa Pharmaceutical Co Ltd; WO 9606617 A1 1996 HCAPLUS
(23) Neurogen Corp; AU 9943374 A 1999 HCAPLUS
(24) Neurogen Corp; WO 9964425 A1 1999 HCAPLUS
(25) Takeda Chemical Industries Ltd; JP 05229941 A 1993 HCAPLUS
(26) Takeda Chemical Industries Ltd; JP 09221417 A 1997 HCAPLUS
(27) Takeda Chemical Industries Ltd; JP 09315997 A 1997 HCAPLUS
(28) Takeda Chemical Industries Ltd; US 2001006678 A1 1997 HCAPLUS
(29) Takeda Chemical Industries Ltd; CA 2192773 A 1997 HCAPLUS
(30) Takeda Chemical Industries Ltd; CA 2241322 A 1997 HCAPLUS
(31) Takeda Chemical Industries Ltd; US 6190700 B1 1997 HCAPLUS
(32) Takeda Chemical Industries Ltd; US 6190702 B1 1997 HCAPLUS
(33) Takeda Chemical Industries Ltd; EP 781548 A2 1997 HCAPLUS
(34) Takeda Chemical Industries Ltd; EP 781548 A3 1997 HCAPLUS
(35) Takeda Chemical Industries Ltd; EP 781548 B1 1997 HCAPLUS
(36) Takeda Chemical Industries Ltd; EP 889722 A2 1997 HCAPLUS
(37) Takeda Chemical Industries Ltd; AU 9720432 A1 1997 HCAPLUS
(38) Takeda Chemical Industries Ltd; WO 9735563 A2 1997 HCAPLUS
(39) Takeda Chemical Industries Ltd; WO 9735563 A3 1997 HCAPLUS
(40) Takeda Chemical Industries Ltd; JP 10130271 A 1998 HCAPLUS
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(44) Takeda Chemical Industries Ltd; JP 10203982 A 1998 HCAPLUS
(45) Takeda Chemical Industries Ltd; CN 1172644 A 1998 HCAPLUS
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(58) Takeda Chemical Industries Ltd; WO 9815263 A2 1998 HCAPLUS
(59) Takeda Chemical Industries Ltd; EP 1049458 A1 1999 HCAPLUS
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(64) Takeda Chemical Industries Ltd; WO 9937288 A1 1999 HCAPLUS
(65) Takeda Chemical Industries Ltd; WO 0174823 A2 2001 HCAPLUS
(66) Takeda Chemical Industries Ltd; WO 0174823 A3 2001 HCAPLUS
(67) Takeda Chemical Industries Ltd; WO 0189521 A1 2001 HCAPLUS
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(69) Takeda Chemical Industries Ltd; JP 200247184 A 2001
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IT **9004-32-4**, Carboxymethyl cellulose
RL: NUU (Other use, unclassified); USES (Uses)
(as wetting agents in producing fine granulate drug with solvents)

RN 9004-32-4 HCAPLUS

CN Cellulose, carboxymethyl ether, sodium salt (8CI, 9CI) (CA INDEX NAME)

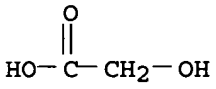
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

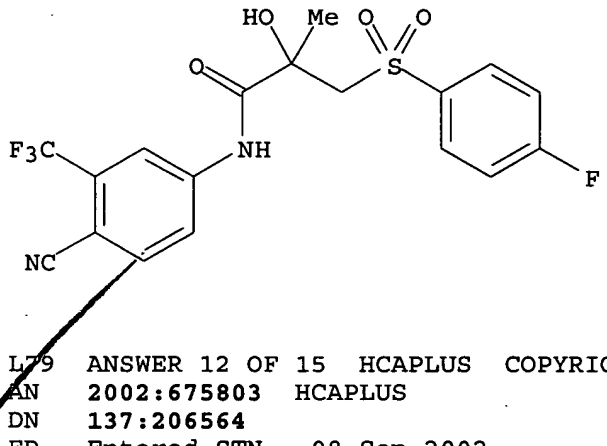
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 79-14-1
CMF C2 H4 O3



IT **90357-06-5, Bicalutamide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(wetting agents in producing fine granulate drug with solvents)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



LT9 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:675803** HCAPLUS
DN **137:206564**
ED Entered STN: 08 Sep 2002
TI Pharmaceutical formulation comprising **bicalutamide** and an enteric polymer
IN Bateman, Nicola; Cahill, Julie
PA Astrazeneca AB, Swed.; Astrazeneca UK Limited
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002067893	A2	20020906	WO 2002-GB766	20020222 <--
WO 2002067893	A3	20030116		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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CA 2439366	AA	20020906	CA 2002-2439366	20020222	<--
EP 1368001	A2	20031210	EP 2002-712105	20020222	<--
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JP 2004143185	A2	20040520	JP 2004-41583	20040218	<--
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CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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GB 2372444	ECLA	A61K009/00M18D; A61K031/167; A61K031/277; A61K047/38<--
JP 2004521918	FTERM	4C076/AA31; 4C076/AA45; 4C076/BB01; 4C076/CC27; 4C076/EE09J; 4C076/EE31J; 4C076/EE32J; 4C076/EE33J; 4C076/FF25; 4C076/FF31; 4C206/AA01; 4C206/AA02; 4C206/JA04; 4C206/MA02; 4C206/MA05; 4C206/MA55; 4C206/MA61; 4C206/MA72; 4C206/NA12; 4C206/ZB26 <--
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AB The present invention relates to a pharmaceutical formulation comprising **bicalutamide** and an enteric polymer having a pKa from 3 to 6. The invention also relates to a daily pharmaceutical dose of **bicalutamide** provided by such a formulation. In addition, the invention relates to the use of such an enteric polymer in solid dispersion with **bicalutamide** for increasing the bioavailability of the **bicalutamide**; for reducing inter-patient variability in plasma concns. of **bicalutamide**; or for treating and/or reducing the risk of prostate cancer in a patient. Solid dispersion compns. containing **bicalutamide** and polymers such as hydroxypropyl Me cellulose phthalate or Eudragits were prepared

ST **bicalutamide** solid dispersion pharmaceutical polymer

IT Antitumor agents
Drug bioavailability
Human
Prostate gland, neoplasm
Wetting agents
(pharmaceutical formulation comprising **bicalutamide** and an enteric polymer)

IT Drug delivery systems
(solid dispersions; pharmaceutical formulation comprising **bicalutamide** and an enteric polymer)

IT Drug delivery systems
(tablets; pharmaceutical formulation comprising **bicalutamide** and an enteric polymer)

IT 25086-15-1, Eudragit L 100
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Eudragit S 100; pharmaceutical formulation comprising **bicalutamide** and an enteric polymer)

IT **9004-38-0**, Cellulose acetate phthalate **9050-31-1**, Hydroxypropyl methyl cellulose phthalate 25212-88-8, Eudragit L 30D55 **39340-12-0**, Hydroxypropyl methyl cellulose trimellitate **52907-01-4**, Cellulose acetate trimellitate 53237-50-6 **54391-89-8**, Cellulose acetate terephthalate **58858-21-2**, Hydroxypropyl methyl cellulose acetate **61811-44-7**, Hydroxypropyl methyl cellulose acetate phthalate **71138-97-1**, Hydroxypropyl methyl cellulose acetate succinate **89233-51-2**, Cellulose propionate phthalate **93792-59-7**, Hydroxypropyl methyl cellulose succinate **167077-74-9**, Cellulose propionate trimellitate **167077-75-0**, Cellulose butyrate trimellitate **188979-58-0**, Hydroxypropyl cellulose acetate phthalate **288141-80-0**, Methyl cellulose acetate phthalate **288156-14-9**, Hydroxypropyl methyl cellulose acetate trimellitate **288307-50-6**, Hydroxypropyl cellulose butyrate phthalate **288307-51-7**, Cellulose acetate isophthalate **288372-69-0**, Ethyl cellulose acetate phthalate **288372-70-3**, Hydroxypropyl cellulose acetate phthalate succinate **288372-71-4**, Methyl cellulose acetate trimellitate **288372-72-5**, Ethyl cellulose acetate trimellitate **288372-73-6**, Hydroxypropyl cellulose acetate trimellitate **288372-74-7**, Hydroxypropyl cellulose acetate trimellitate succinate
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation comprising **bicalutamide** and an enteric polymer)

IT **90357-06-5**, **Bicalutamide**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation comprising **bicalutamide** and an enteric polymer)

IT **9004-38-0**, Cellulose acetate phthalate **9050-31-1**, Hydroxypropyl methyl cellulose phthalate **39340-12-0**, Hydroxypropyl methyl cellulose trimellitate **52907-01-4**, Cellulose acetate trimellitate **54391-89-8**, Cellulose acetate terephthalate **58858-21-2**, Hydroxypropyl methyl cellulose acetate **61811-44-7**, Hydroxypropyl methyl cellulose acetate phthalate **71138-97-1**, Hydroxypropyl methyl cellulose acetate succinate **89233-51-2**, Cellulose propionate phthalate **93792-59-7**, Hydroxypropyl methyl cellulose succinate **167077-74-9**, Cellulose propionate trimellitate **167077-75-0**, Cellulose butyrate trimellitate **188979-58-0**, Hydroxypropyl cellulose acetate phthalate **288141-80-0**, Methyl cellulose acetate phthalate **288156-14-9**, Hydroxypropyl methyl cellulose acetate trimellitate **288307-50-6**, Hydroxypropyl cellulose butyrate phthalate **288307-51-7**, Cellulose acetate isophthalate **288372-69-0**, Ethyl cellulose acetate phthalate **288372-70-3**, Hydroxypropyl cellulose acetate phthalate succinate **288372-71-4**, Methyl cellulose acetate trimellitate **288372-72-5**, Ethyl cellulose acetate trimellitate **288372-73-6**, Hydroxypropyl cellulose acetate trimellitate **288372-74-7**, Hydroxypropyl cellulose acetate trimellitate succinate

RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation comprising **bicalutamide** and an enteric polymer)

RN 9004-38-0 HCAPLUS
CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate (9CI) (CA INDEX NAME)

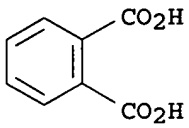
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 88-99-3
CMF C8 H6 O4



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CRN 64-19-7
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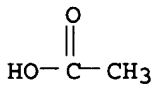


RN 9050-31-1 HCAPLUS
CN Cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

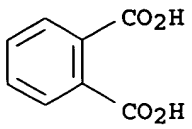
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 88-99-3
CMF C8 H6 O4

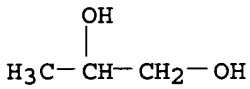


CM 3

CRN 67-56-1
CMF C H4 O

CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 39340-12-0 HCAPLUS
CN Cellulose, 1,2,4-benzenetricarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

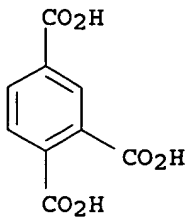
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

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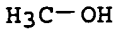
CMF C H4 O



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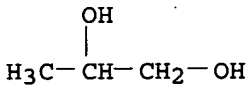
CMF C3 H8 O2



RN 52907-01-4 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)

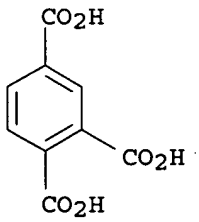
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 528-44-9
CMF C9 H6 O6



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CRN 64-19-7
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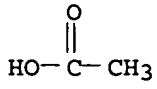


RN 54391-89-8 HCAPLUS
CN Cellulose, acetate hydrogen 1,4-benzenedicarboxylate (9CI) (CA INDEX NAME)

CM 1

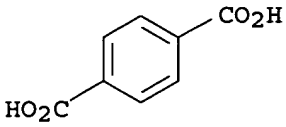
CRN 9004-34-6

CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-21-0
CMF C8 H6 O4



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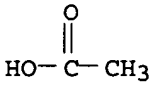

RN 58858-21-2 HCAPLUS
CN Cellulose, acetate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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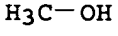
CRN 67-56-1
CMF C H4 O



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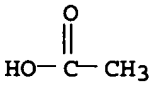
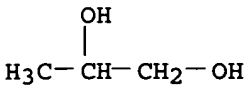


CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 61811-44-7 HCAPLUS
CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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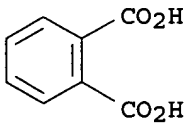
CRN 88-99-3
CMF C8 H6 O4



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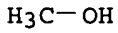

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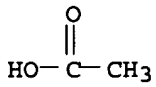

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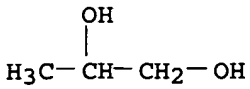
CMF C3 H8 O2



RN 71138-97-1 HCAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate (9CI) (CA INDEX NAME)

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CRN 110-15-6
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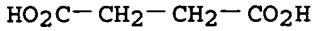


CM 2

CRN 64-19-7
CMF C2 H4 O2

CM 3

CRN 9004-65-3
CMF C3 H8 O2 . x C H4 O . x Unspecified

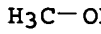
CM 4

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

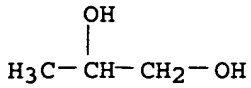
CM 5

CRN 67-56-1
CMF C H4 O



CM 6

CRN 57-55-6
CMF C3 H8 O2



RN 89233-51-2 HCAPLUS
CN Cellulose, hydrogen 1,2-benzenedicarboxylate propanoate (9CI) (CA INDEX NAME)

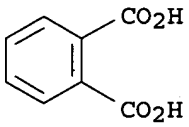
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

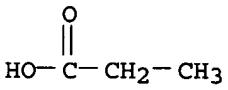
CM 2

CRN 88-99-3
CMF C8 H6 O4



CM 3

CRN 79-09-4
CMF C3 H6 O2



RN 93792-59-7 HCAPLUS
CN Cellulose, butanedioate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)

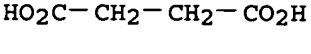
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

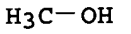
CM 2

CRN 110-15-6
CMF C4 H6 O4



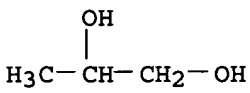
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 167077-74-9 HCAPLUS
CN Cellulose, dihydrogen 1,2,4-benzenetricarboxylate propanoate (9CI) (CA INDEX NAME)

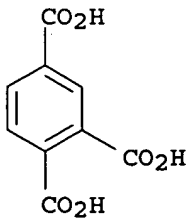
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

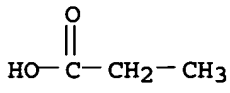
CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

CRN 79-09-4
CMF C3 H6 O2



RN 167077-75-0 HCAPLUS
CN Cellulose, butanoate dihydrogen 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)

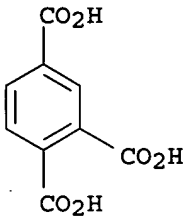
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

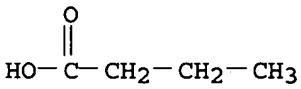
CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

CRN 107-92-6
CMF C4 H8 O2



RN 188979-58-0 HCAPLUS
CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

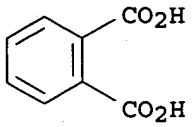
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

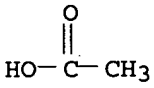
CM 2

CRN 88-99-3
CMF C8 H6 O4



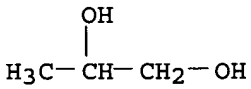
CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 288141-80-0 HCAPLUS
CN Cellulose, acetate 1,2-benzenedicarboxylate, methyl ether (9CI) (CA INDEX NAME)

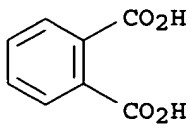
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

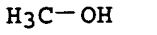
CM 2

CRN 88-99-3
CMF C8 H6 O4



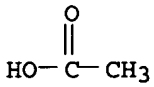
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

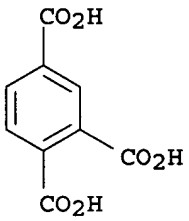
CRN 64-19-7
CMF C2 H4 O2



RN 288156-14-9 HCAPLUS
CN Cellulose, 2-hydroxypropyl methyl ether, acetate 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)

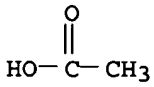
CM 1

CRN 528-44-9
CMF C9 H6 O6



CM 2

CRN 64-19-7
CMF C2 H4 O2



CM 3

CRN 9004-65-3
CMF C3 H8 O2 . x C H4 O . x Unspecified

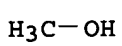
CM 4

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

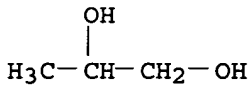
CM 5

CRN 67-56-1
CMF C H4 O



CM 6

CRN 57-55-6
CMF C3 H8 O2



RN 288307-50-6 HCAPLUS
CN Cellulose, 1,2-benzenedicarboxylate butanoate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

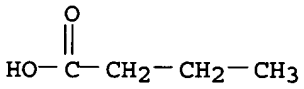
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

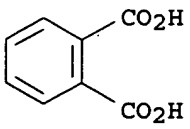
CM 2

CRN 107-92-6
CMF C4 H8 O2



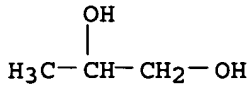
CM 3

CRN 88-99-3
CMF C8 H6 O4



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 288307-51-7 HCAPLUS
CN Cellulose, acetate 1,3-benzenedicarboxylate (9CI) (CA INDEX NAME)

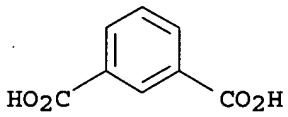
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

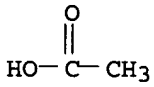
CM 2

CRN 121-91-5
CMF C8 H6 O4



CM 3

CRN 64-19-7
CMF C2 H4 O2



RN 288372-69-0 HCAPLUS
CN Cellulose, acetate 1,2-benzenedicarboxylate, ethyl ether (9CI) (CA INDEX NAME)

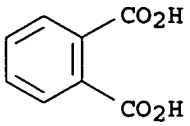
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

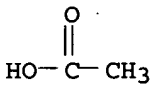
CM 2

CRN 88-99-3
CMF C8 H6 O4



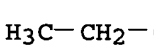
CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 64-17-5
CMF C2 H6 O



RN 288372-70-3 HCAPLUS
CN Cellulose, acetate 1,2-benzenedicarboxylate butanedioate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

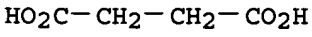
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

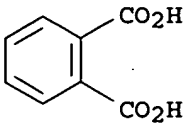
CM 2

CRN 110-15-6
CMF C4 H6 O4



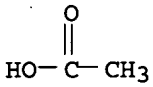
CM 3

CRN 88-99-3
CMF C8 H6 O4



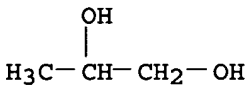
CM 4

CRN 64-19-7
CMF C2 H4 O2



CM 5

CRN 57-55-6
CMF C3 H8 O2



RN 288372-71-4 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate, methyl ether (9CI) (CA INDEX NAME)

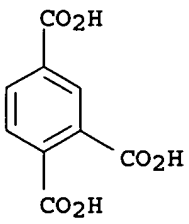
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

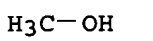
CM 2

CRN 528-44-9
CMF C9 H6 O6



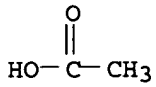
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 64-19-7
CMF C2 H4 O2



RN 288372-72-5 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate, ethyl ether (9CI) (CA INDEX NAME)

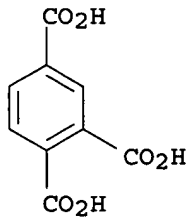
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

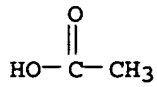
CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

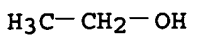
CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 64-17-5

CMF C2 H6 O



RN 288372-73-6 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

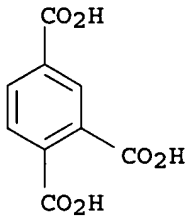
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

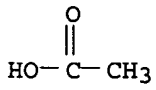
CM 2

CRN 528-44-9
CMF C9 H6 O6



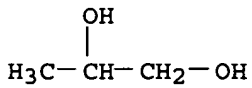
CM 3

CRN 64-19-7
CMF C2 H4 O2



CM 4

CRN 57-55-6
CMF C3 H8 O2



RN 288372-74-7 HCAPLUS
CN Cellulose, acetate 1,2,4-benzenetricarboxylate butanedioate, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)

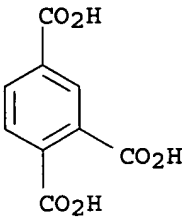
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

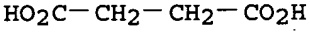
CM 2

CRN 528-44-9
CMF C9 H6 O6



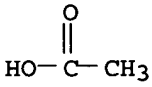
CM 3

CRN 110-15-6
CMF C4 H6 O4



CM 4

CRN 64-19-7
CMF C2 H4 O2



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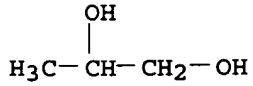
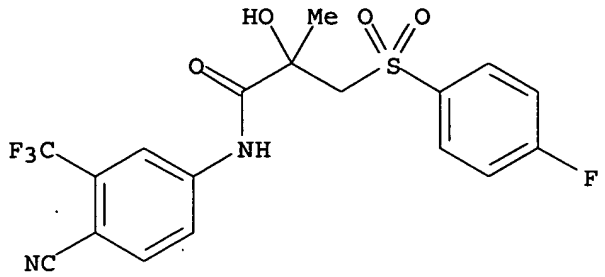
CRN 57-55-6
CMF C3 H8 O2



IT **90357-06-5, Bicalutamide**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation comprising **bicalutamide** and an enteric polymer)
RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



L79 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:585298** HCAPLUS
DN **137:384621**
ED Entered STN: 06 Aug 2002
TI Novel nonsteroidal ligands with high binding affinity and potent functional activity for the androgen receptor
AU He, Yali; Yin, Donghua; Perera, Minoli; Kirkovsky, Leonid; Stourman, Nina; Li, Wei; Dalton, James T.; Miller, Duane D.
CS College of Pharmacy, Department of Pharmaceutical Sciences, University of Tennessee-Memphis, Memphis, TN, 38163, USA
SO European Journal of Medicinal Chemistry (**2002**), 37(8), 619-634
CODEN: EJMCA5; ISSN: 0223-5234
PB Editions Scientifiques et Medicales Elsevier
DT Journal
LA English
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 7, 32
OS CASREACT 137:384621
AB While nonsteroidal androgen receptor (AR) antagonists have been known for many years, and used in the clinic for the treatment of hormone dependent prostate cancer, very little is known about nonsteroidal AR agonists. A series of chiral **bicalutamide** analogs, which bear electron-withdrawing groups (either a cyano or a nitro group at the 4-position and a trifluoromethyl group at the 3-position) in the aromatic A ring, and different substituents at the para position in the aromatic B ring of the parent mol. was designed and synthesized. A series of **racemic bicalutamide** analogs, which have a trifluoromethyl group instead of a Me group at the R2 position were also synthesized. AR binding affinities of our compds. in a competitive binding assay with a radiolabeled high affinity AR ligand, 3H-mibolerone, their abilities to stimulate AR-mediated transcriptional activation in a cotransfection assay were examined These studies demonstrated that (1) nonsteroidal ligands can be structurally modified from known nonsteroidal antiandrogens to generate ligands capable of activating AR-mediated transcriptional activation. (2) R-isomer analogs exhibit higher AR binding affinity and more potent functional activity than their corresponding S-isomers in all cases. (3) All sulfide analogs show higher AR binding affinity and more potent functional activity than their corresponding sulfone analogs, with the exception of ligand R-8. Those ligands which exhibit high AR binding affinity and potent functional activity for human AR may provide effective clin. uses for male fertility, male contraception, and hormone replacement therapy.
ST androgen receptor agonist nonsteroidal asym prepn; structure activity androgen receptor binding nonsteroidal agonist
IT **Structure-activity relationship**
(adrenergic agonist; preparation of non-steroidal ligands from a chiral

3-bromo-2-hydroxy-2-methylpropanamide and evaluation of their affinity for the androgen receptor)

IT Steroids, preparation
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(nonsteroidal analogs; preparation of non-steroidal ligands from a chiral 3-bromo-2-hydroxy-2-methylpropanamide and evaluation of their affinity for the androgen receptor)

IT Asymmetric synthesis and induction
Human
(preparation of non-steroidal ligands from a chiral 3-bromo-2-hydroxy-2-methylpropanamide and evaluation of their affinity for the androgen receptor)

IT Androgen receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of non-steroidal ligands from a chiral 3-bromo-2-hydroxy-2-methylpropanamide and evaluation of their affinity for the androgen receptor)

IT 216665-15-5P 216665-18-8P 216665-38-2P 216665-40-6P 216665-49-5P
216665-66-6P 247090-61-5P 261904-44-3P 476314-36-0P 476314-37-1P
476314-38-2P 476314-39-3P 476314-40-6P 476314-51-9P 476314-54-2P
476314-55-3P
RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of non-steroidal ligands from a chiral 3-bromo-2-hydroxy-2-methylpropanamide and evaluation of their affinity for the androgen receptor)

IT 90356-30-2P 206193-16-0P 216665-35-9P 216665-55-3P 216665-73-5P
476314-41-7P 476314-44-0P 476314-45-1P 476314-46-2P 476314-50-8P
476314-52-0P 476314-53-1P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of non-steroidal ligands from a chiral 3-bromo-2-hydroxy-2-methylpropanamide and evaluation of their affinity for the androgen receptor)

IT 79-03-8, Propionyl chloride 393-11-3 431-35-6 654-70-6 1193-02-8, 4-Aminothiophenol 13113-79-6, 4-Nitrothiophenol sodium salt
113181-02-5 206193-17-1 206193-18-2 216665-24-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of non-steroidal ligands from a chiral 3-bromo-2-hydroxy-2-methylpropanamide and evaluation of their affinity for the androgen receptor)

IT 90357-36-1P 90357-44-1P 476314-47-3P 476314-48-4P 476314-49-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of non-steroidal ligands from a chiral 3-bromo-2-hydroxy-2-methylpropanamide and evaluation of their affinity for the androgen receptor)

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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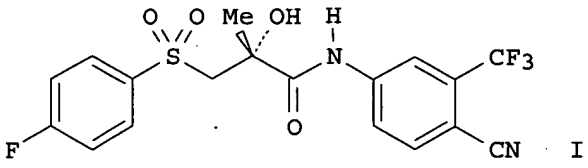
(23) Tucker, H; J Med Chem 1988, V31, P954 HCAPLUS

L79 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:509907** HCAPLUS
DN **137:384623**
ED Entered STN: 09 Jul 2002
TI Syntheses of enantiomerically pure (R)- and (S)-**bicalutamide**
AU James, Kenneth D.; Ekwuribe, Nnochiri N.
CS Department of Innovation, Nobex Corporation, Durham, NC, 27713, USA
SO Tetrahedron (**2002**), 58(29), 5905-5908
CODEN: TETRAB; ISSN: 0040-4020
PB Elsevier Science Ltd.
DT Journal
LA English
CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
OS CASREACT 137:384623
GI



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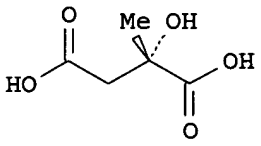

II

AB The **racemic** antiandrogen **bicalutamide** is the leading antiandrogen used for the treatment of prostate cancer. The (R)-isomer possesses virtually all of the activity, but both isomers are metabolized by the liver. A convenient synthetic route to the active enantiomer would be an attractive option for patients who are hepatically impaired. We now demonstrate a rather short synthesis of (R)-**bicalutamide** (I), starting with naturally occurring (S)-citramalic acid (II). The authors have also used this procedure to synthesized the less active (S)-**bicalutamide** from the unnatural (R)-citramalic acid.
ST asym synthesis **bicalutamide**
IT Asymmetric synthesis and induction
(syntheses of enantiomerically pure (R)- and (S)-**bicalutamide**
)
IT 115-17-3, Bromal 371-42-6, 4-Fluorobenzenethiol 654-70-6,

4-Amino-2-trifluoromethylbenzonitrile 6236-09-5 6236-10-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(syntheses of enantiomerically pure (R)- and (S)-**bicalutamide**
)

IT 90357-17-8P 335595-47-6P 335595-50-1P 335595-52-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(syntheses of enantiomerically pure (R)- and (S)-**bicalutamide**
)

IT **113299-38-0P 113299-40-4P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(syntheses of enantiomerically pure (R)- and (S)-**bicalutamide**
)

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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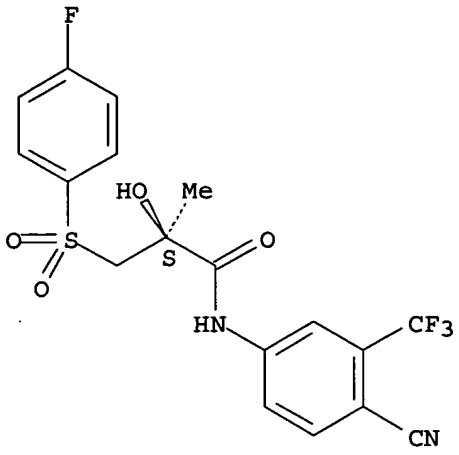
(19) Tucker, H; J Med Chem 1988, V31, P885 HCAPLUS
(20) Tucker, H; J Med Chem 1988, V31, P954 HCAPLUS
(21) Tyrrell, C; Eur Urol 1998, V33, P39 HCAPLUS
(22) Tyrrell, C; Eur Urol 1998, V33, P447 HCAPLUS

IT **113299-38-0P 113299-40-4P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(syntheses of enantiomerically pure (R)- and (S)-**bicalutamide**
)

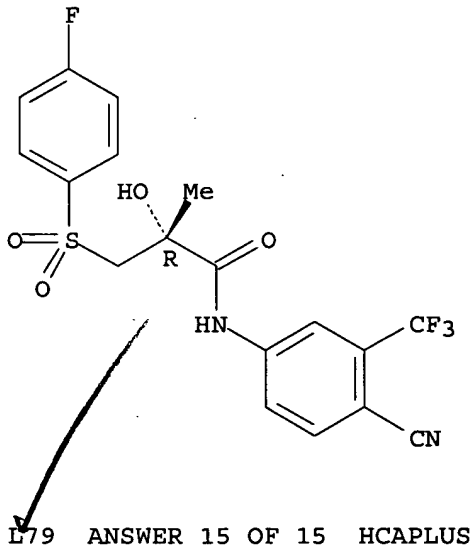
RN 113299-38-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L79 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:202221** HCAPLUS
ED Entered STN: 22 Mar 2001
TI Asymmetric synthesis of the antiandrogen (R)-**bicalutamide**
AU James, Kenneth D., Jr.; Ekwuribe, Nnochiri
CS Chemical Innovation and Drug Discovery, Nobex Corporation, Research Triangle Park, NC, 27709, USA
SO Abstracts of Papers, 221st ACS National Meeting, San Diego, CA, United States, April 1-5, 2001 (**2001**) MEDI-314
CODEN: 69FZD4
PB American Chemical Society
DT Journal; Meeting Abstract
LA English
AB The non-steroidal, antiandrogen (R, S)-**bicalutamide**, which is sold under the name **Casodex**-, is the leading compound for the treatment of prostate cancer in combination with LHRH agonists. **Casodex**- is sold as the **racemic** mixture but virtually all the desired activity resides in the (R)-enantiomer, which has a longer half-life in vivo and greater binding affinity to the androgen receptor.

A pure (R)-**bicalutamide** may be clin. useful, but the only known asym. synthesis of (R)-**bicalutamide** utilizes the com. expensive, unnatural amino acid D-proline as a chiral auxiliary. We describe the synthesis of pure (R)-**bicalutamide** in five steps starting from an inexpensive, naturally occurring chiral compound that generates the desired enantiomer in high yield.

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    FOR DETAILS. <<<

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L106 ANSWER 1 OF 19  WPIX  COPYRIGHT 2005 THE THOMSON CORP on STN
AN   2005-132501 [14]   WPIX
DNC  C2005-043706
TI   Purification and isolation of bicalutamide by solution
     crystallization comprises combining crude bicalutamide
     and solvent, crystallizing bicalutamide from solvent
     and collecting crystals.
DC   B05
IN   DOLITZKY, B; REANY, O; SHAMMAI, J
PA   (BIOG) BIOGAL GYOGYSZERGYAR RT; (TEVA-N) TEVA PHARM USA INC
CYC  104
PI   WO 2005009946   A1 20050203 (200514)* EN   21    C07C315-06
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            LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
            PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN
            YU ZA ZM ZW
ADT  WO 2005009946 A1 WO 2003-US20307 20030625
PRAI WO 2003-US20307      20030625
IC   ICM  C07C315-06
AB   WO2005009946 A UPAB: 20050228
     NOVELTY - Method (M1) of purification and isolation of
```

bicalutamide by solution **crystallization** comprises:
(i) combining crude **bicalutamide** and a solvent (A);
(ii) **crystallizing** the **bicalutamide** from (A); and
(iii) collecting the **crystals** of **bicalutamide.**
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(a) a method (M2) of purification and isolation of **bicalutamide** by solution **crystallization** comprising:
(1) combining the crude **bicalutamide** and a first solvent (A1);
(2) adding a second solvent (A2) to the crude **bicalutamide** -first solvent mixture; and
(3) steps (ii) and (iii) as above; and
(b) a method (M3) of purification and isolation of **bicalutamide** comprising:
(A) combining the crude **bicalutamide** and a first solvent (A3) where (A3) is an antisolvent;
(B) adding a second solvent (A4) to the crude **bicalutamide** -(A3) mixture; and
(C) steps (ii) and (iii) as before.
ACTIVITY - None given.
MECHANISM OF ACTION - Antiandrogen.
USE - For purification and isolation of **bicalutamide**, useful as an anti-androgenic compound to decrease the testosterone level without influencing the regulation mechanisms of the hypothalamus.
ADVANTAGE - The method uses a solvent system which has low toxic potential and is of lower risk to human health.
Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B10-A10; B11-B; **B12-M11H**; B14-D02A5
TECH UPTX: 20050228
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: Step (ii) involves seeding the **bicalutamide** suspension. (M2) Further involves heating the resulting **bicalutamide** solution to the boiling point of the solvent. The solution of step (1) is heated to the boiling point of (A1) and the addition of (A2) and (A4) takes place under reflux conditions. Step (ii) involves cooling the **bicalutamide** solution to a temperature of 25 degrees C. (M2) Further involves following addition of (A2), adding sufficient volume of (A1) to dissolve the at least partially desolubilized **bicalutamide.** The amount of (A2) is added in an amount sufficient to bring at least partially desolubilized **bicalutamide.** (M3) further involves heating the solution formed in step (A) to the boiling point of (A3).
Preferred Components: (A) Is selected from water, methanol, ethanol, dichloromethane, toluene, PE, chloroform, hexane, 1,2-dichloroethane, diethyl ether, propanol or isopropanol (preferably ethanol, propanol or isopropanol). (A1) and (A2) are selected from water, methanol, ethanol, ethyl acetate, acetonitrile, acetone, tetrahydrofuran (THF), propanol, N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO) or isobutyl methyl ketone (preferably ethanol, ethyl acetate, acetone, THF, propanol, DMSO or isobutyl methyl ketone). (A2) Is an anti-solvent. (A1):(A2) system is DMF:water or (A1) is ethanol and (A2) is water. (A3) is toluene, ether, chloroform, water or methanol and (A4) is acetonitrile or (A3) is water and (A4) is acetone and THF or (A3) Is methanol and (A4) is acetone, THF, DMF or (A3) is ethanol and (A4) is THF, DMF or isobutyl methyl ketone.
ABEX UPTX: 20050228
EXAMPLE - Crude **bicalutamide** (260 g) was dissolved in ethanol (5 l) at reflux temperature and water (7.5 l) was added gradually over 1.5-2 hours to precipitate the product. The slurry was cooled to 0-5 degrees C and stirred for 2 hours. The precipitate was collected, washed with water (625 ml) and dried at 60 degrees C to yield the **crystalline** **bicalutamide** (94%) having purity of 99.94%.

L106 ANSWER 2 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2005-039300 [04] WPIX
DNC C2005-013028
TI New **crystalline bicalutamide** (4'-cyano-3-((4-fluorophenyl)sulfonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide) useful to treat androgen disorders and prostate cancer.
DC A96 B05
IN CUCALA, E J; SILES, O A; CUCALA ESCOI, J; SILES ORTEGA, A
PA (CUCA-I) CUCALA E J; (SILE-I) SILES O A; (SYNT-N) **SYNTHON BV**
CYC 108
PI WO 2004100944 A1 20041125 (200504)* EN 41 A61K031-277
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W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2005008691 A1 20050113 (200506) A61K009-48 <--
ADT WO 2004100944 A1 WO 2004-EP5189 20040513; US 2005008691 A1 Provisional US 2003-470224P 20030514, US 2004-842632 20040511
PRAI US 2003-470224P 20030514; US 2004-842632 20040511
IC ICM **A61K009-48**; A61K031-277
ICS **A61K009-14**; **A61K009-16**; A61K009-20; A61P013-08
AB WO2004100944 A UPAB: 20050117
NOVELTY - **Crystalline bicalutamide** (I) (at least 99% pure and is in particulate form having an average particle size of 0.1-20 microns; a bulk density of 1.3-1.6 mg/ml; or a specific surface area of at least 0.6 m2/g) is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for
(1) a granulate comprising at least 50% (I) and at least one pharmaceutically acceptable excipient;
(2) a pharmaceutical composition comprising the granulate and an auxiliary excipient where the auxiliary excipient comprises up to 25% of the pharmaceutical composition;
(3) a solid oral dosage form comprising at least 40% (I) and at least one pharmaceutically acceptable excipient; and
(4) a process (II) that comprises granulating a mixture comprising (I) and at least one pharmaceutically acceptable excipient to form a granulate comprising at least 50 (w/w)% of (I).
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - None given.
USE - (I) is useful to treat androgen disorder (claimed). (I) is also useful to treat prostate cancer. No biological data given.
ADVANTAGE - The pharmaceutical compositions containing high amounts of (I) exhibit good drug release properties/profiles.
Dwg.0/6
FS CPI
FA AB; DCN
MC CPI: A12-V01; B04-C03A; B10-A10; B12-M11B; B12-M11C; B12-M11D; **B12-M11H**; B14-D01A; B14-D02A5; B14-H01U
TECH UPTX: 20050117
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No general methods for the preparation of (I) are given.
Preferred Compound: (I) have an average particle size within the range of 1-10 microns and a specific surface area of at least 3 m2 /g. The granulate comprises 60-90% of (I). The pharmaceutically acceptable excipient is polyvinylpyrrolidone or a fatty acid ester.
Preferred Process: (II) further comprises forming the mixture by combining an appropriate amount of micronized (I) and at least one excipient comprises a melt granulation excipient (such as binders, disintegrants or wetting surface-active agents). The granulating comprises wet granulation,

roll-compacting or milling the mixture; and the granulating occurs without an organic solvent. At least one pharmaceutically acceptable excipient comprises a melt granulation excipient, and where the granulating comprises melt-granulating the mixture. (II) further comprises filling the granulate into capsules, optionally with auxiliary excipients; and blending the granulate with at least one auxiliary excipient and tabletting the blend.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The granulate further comprises a surfactant and the granulate was formed using micronized **bicalutamide.** The composition is a unit dosage form of a capsule or a tablet. The capsule and tablet contains 20-200 mg of (I). The dosage form exhibits a dissolution profile in vitro such that at 30 minutes at least 75% of (I) has been released. The solid oral dosage form comprises 50-80% of (I).

ABEX UPTX: 20050117

ADMINISTRATION - Administration of (I) is oral (claimed). No dosage is given.

EXAMPLE - **Bicalutamide** (2.15 g) and ethyl acetate (19.5 ml) were transferred into a round bottomed 3 neck flask of 250 ml. The suspension was heated to reflux in an oil bath and stirred with magnetic stirrer and stirrer device. Reflux was maintained until a clear solution was obtained. The solution was cooled to 20degreesC in a water bath while kept stirring. During cooling the **bicalutamide crystallized.** The suspension was worked up to give **crystalline** form I of **bicalutamide.**

L106 ANSWER 3 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-776466 [77] WPIX
DNC C2004-272007
TI Combination of levogyrate **bicalutamide.**
DC B05
IN SHI, M; WANG, L; XUE, Y
PA (HUAT-N) HUATUO MEDICINE SCI TECH DEV CO LTD
CYC 1
PI CN 1518977 A 20040811 (200477)* A61K031-16
ADT CN 1518977 A CN 2003-115155 20030124
PRAI CN 2003-115155 20030124
IC ICM A61K031-16
ICS **A61K009-14**; A61P013-08; A61P035-00
AB CN 1518977 A UPAB: 20041203
NOVELTY - A L-Bikaluan composition, its **crystal** type suitable for preparing the orally applied medicine, the process for preparing its **crystal**, the granularity and smelting point of said **crystal**, and the application of said composition in preparing medicines for treating prostatic cancer are disclosed.
Dwg.0/0
FS CPI
FA AB
MC CPI: B10-A10; B10-A15; B10-D03; B10-H02A; B10-H02B; B11-B; B14-H01; B14-N07A

L106 ANSWER 4 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-652929 [63] WPIX
DNC C2004-233631
TI New **crystalline** form of **bicalutamide** for use in treatment of prostate cancer, has specified powder X-ray diffraction pattern with characteristic interplanar spacings.
DC B05
IN NARASA, R A; NARASA, R B; PARTHASARADHI, R B; RAJI, R R; RATHNAKAR, R K
PA (HETE-N) HETERO DRUGS LTD; (NARA-I) NARASA R A; (NARA-I) NARASA R B; (PART-I) PARTHASARADHI R B; (RAJI-I) RAJI R R; (RATH-I) RATHNAKAR R K

CYC 102
PI WO 2004074350 A2 20040902 (200463)* EN 11 C08J000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA
ZM ZW
AU 2003209667 A1 20040909 (200501) C08J000-00
US 2005020675 A1 20050127 (200509) C07C255-60
ADT WO 2004074350 A2 WO 2003-IN35 20030221; AU 2003209667 A1 AU 2003-209667 20030221, WO 2003-IN35 20030221; US 2005020675 A1 WO 2003-IN35 20030221, US 2003-450103 20030610
FDT AU 2003209667 A1 Based on WO 2004074350
PRAI WO 2003-IN35 20030221
IC ICM C07C255-60; C08J000-00
ICS A61K031-277
AB WO2004074350 A UPAB: 20041001
NOVELTY - A new **crystalline** form of **bicalutamide** has a specified powder X-ray diffraction pattern with characteristic interplanar spacings.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(a) preparation of new **crystalline** form of **bicalutamide**;
(b) **amorphous bicalutamide** having a specified characteristic X-ray powder diffraction and broad X-ray diffraction maxima at 10-35 deg. 2 theta ;
(c) preparation of **amorphous bicalutamide** by either heating **bicalutamide** obtained by a known process or **crystalline** form of **bicalutamide** to melt, cooling the mass to 25-35 deg. C, and crushing the resultant flakes to give **amorphous bicalutamide**; or mixing **bicalutamide** and solvent (e.g. 1-3C alcohol or 1-6C ketone) in specified proportion, slurrying for 1-5 hours, and spray or vacuum drying to give **amorphous bicalutamide**; and
(d) a pharmaceutical composition comprising **amorphous** or **crystalline bicalutamide** and a carrier.
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - None given.
USE - For use in treatment of prostate cancer.
ADVANTAGE - The new **crystalline** form of **bicalutamide** is pure, stable, and consistently reproducible.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B10-A10; **B12-M11H**; B14-H01
TECH UPTX: 20041001
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: A **bicalutamide crystalline** form is prepared by dissolving **bicalutamide** obtained by a known process in a solvent (e.g. 1-3C alcohol or 1-6C ketone); maintaining the solution at 0-40 degrees (preferably 25-30 degrees C) for 5-36 (preferably 20-25) hours, optionally seeding with **bicalutamide crystalline** form; and filtering and drying the **crystals** formed to give **bicalutamide crystalline** form.
Preferred Components: The solvent is ethanol or acetone.
ABEX UPTX: 20041001
EXAMPLE - m-Chloroperbenzoic acid (3 g, 85% strength) was added to a stirred solution of N-(4-cyano-3-(trifluoromethyl)phenyl)-3-((4-fluorophenyl)thio)-2-hydroxy-2-methylpropanamide (2.7 g) in methylene dichloride (450 ml). The reaction mixture was stirred at room temperature for 16 hours, washed with saturated sodium sulfite solution (100 ml),

aqueous sodium carbonate solution and brine, and dried with sodium sulfate. The solid obtained upon removal of solvent was **crystallized** from ethyl acetate and petroleum ether to give **bicalutamide** (2.5 g). **Bicalutamide** (10 g) was dissolved in acetone (50 ml), and the solution was stirred at 25-30 degrees C for 24 hours. The **crystals** formed were filtered and dried under vacuum to give **bicalutamide crystalline** form (8.8 g).

L106 ANSWER 5 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-339374 [31] WPIX
DNC C2004-128760
TI New **polymorphic** forms of **bicalutamide** useful in the treatment of e.g. prostate cancer.
DC A96 B05
IN **WESTHEIM, R J H**
PA (WEST-I) WESTHEIM R J H; (SYNT-N) **SYNTHON BV**
CYC 105
PI US 2004063782 A1 20040401 (200431)* 15 A61K031-277
WO 2004029021 A1 20040408 (200431) EN C07C317-46
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003276026 A1 20040419 (200462) C07C317-46
ADT US 2004063782 A1 Provisional US 2002-413765P 20020927, Provisional US 2003-470223P 20030514, US 2003-660775 20030912; WO 2004029021 A1 WO 2003-EP10933 20030925; AU 2003276026 A1 AU 2003-276026 20030925
FDT AU 2003276026 A1 Based on WO 2004029021
PRAI US 2003-660775 20030912; US 2002-413765P 20020927; US 2003-470223P 20030514
IC ICM A61K031-277; C07C317-46
AB US2004063782 A UPAB: 20040514
NOVELTY - **Polymorphic** forms including **crystalline** form (II) (A1) and **amorphous** form (B1) of **bicalutamide** are new.
DETAILED DESCRIPTION - **Polymorphic** forms including **crystalline** form (II) (A1) and **amorphous** form (B1) of **bicalutamide** are new.
INDEPENDENT CLAIMS are included for following
(1) a composition (C1) comprising (A1), at least one of **crystalline bicalutamide** of form (I), and (B1);
(2) a composition (C2) comprising (A1), and an excipient; and
(3) preparation of the **polymorphic** forms.
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - Androgenic inhibitor.
USE - For treating prostate cancer and having anti-androgenic activity.
ADVANTAGE - The **bicalutamide** of form (II) is isolated in a relatively pure form with at least 98% purity. The **polymorphic** forms exhibit better stability than the prior art excellent antiandrogenic activity and hence are effective for treating prostate cancer.
Dwg.0/8
FS CPI
FA AB; DCN
MC CPI: A12-V01; B04-C02A1; B04-C02A2; B04-C02B2; B07-A02B; B10-A10; B14-D02A; B14-H01; B14-N07A
TECH UPTX: 20040514
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (A1) involves:
(a) Process A: precipitating (A1) from a solution containing

bicalutamide in the presence of seed **crystals** of form (II) by lowering the temperature of the solution and/or contacting with a contrasolvent at least 35 degrees C; and
(b) Process B: heating (B1) to get **crystals** of (A1).
Preparation of (B1) involves heating a solid form of **bicalutamide** to form a melt and cooling the resultant melt.
Preferred Components: Form (II) is characterized by an X-ray diffraction pattern as given in the specification. The **crystalline** form is racemic. The excipient is a carrier or diluent (preferably **microcrystalline** cellulose, hydroxypropyl methylcellulose, lactose or starch).

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The excipient is calcium phosphate.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: (C2) Comprises form (II) (0.1 - 99.9 wt.%). (C2) Is substantially free of the form (I), but optionally comprises the form (I). (C2) Is in an unit dose formulated as solid oral dosage form, solution or suspension.

ABEX UPTX: 20040514

ADMINISTRATION - Administration of (A1) is orally (claimed). Dosage is 0.1 - 125 mg/kg or 1 - 600 (preferably 1 - 300, especially 50 - 150) mg.
EXAMPLE - **Bicalutamide** form (I) (1 g) was heated in an oil bath at 210 degrees C for 5 minutes. The resultant melt was cooled to room temperature; and again heated in the oil bath at 160 degrees C. Within few minutes **crystals** of **bicalutamide** form (II) were formed. The resultant **crystals** (5 mg) were suspended in n-heptane (7 ml) and the suspension was stirred with a magnetic stirrer in a water bath. **Bicalutamide** form (I) (0.5 g) was dissolved in ethyl acetate (7 ml) at reflux. The warm solution was added dropwise to the stirred cold heptane suspension. The resultant milky suspension was filtered under reduced pressure, and dried at ambient temperature under vaccum for 1.5 hours. **Bicalutamide** (190 g) was dissolved in ethyl acetate (2.52 ml) at reflux, and was added to n-heptane (3 ml) which was cooled to -5 to -10 degrees C and seeded with the form (I) (200 mg). The resultant suspension was stirred for 5 minutes, filtered, washed with cold n-heptane, and dried to get **crystalline** **bicalutamide** form (II) (160 g, 99.78% purity).

L106 ANSWER 6 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-118871 [12] WPIX
CR 2004-315002 [29]
DNC C2004-047589
TI Preparation of **bicalutamide**, useful for treating prostate cancer and other androgen dependent conditions, comprises reacting 4-fluorobenzene sulfinic acid salt with reaction partner.
DC B05
IN ETTEMA, G J B; KELTJENS, R; THIJS, L; BOUKE, E G J
PA (SYNT-N) **SYNTHON BV**
CYC 105
PI US 2003073742 A1 20030417 (200412)* 24 A61K031-277
WO 2004031136 A1 20040415 (200426) EN C07C315-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003273965 A1 20040423 (200465) C07C315-00
US 6818766 B2 20041116 (200475) C07D265-34
ADT US 2003073742 A1 US 2002-261492 20021002; WO 2004031136 A1 WO 2003-EP11166 20031001; AU 2003273965 A1 AU 2003-273965 20031001; US 6818766 B2 US

2002-261492 20021002
FDT AU 2003273965 A1 Based on WO 2004031136
PRAI US 2002-261492 20021002
IC ICM A61K031-277; C07C315-00; C07D265-34
ICS C07C255-03; C07C315-04; C07C317-06; C07C317-32; C07C317-46; C07D263-04; C07D317-12
AB US2003073742 A UPAB: 20041122
NOVELTY - Preparation of **bicalutamide** (I) comprises reacting a 4-fluorobenzene sulfinic acid salt (II) with a reaction partner to form (I) and a non **bicalutamide** product (II) and converting (II) to (I).
DETAILED DESCRIPTION - Preparation of **bicalutamide** (I) comprises reacting a 4-fluorobenzene sulfinic acid salt of formula (II) with a reaction partner to form (I) and a non **bicalutamide** product (II) and converting (II) to (I).
Z = a cation.
An INDEPENDENT CLAIM is also included for new compounds of formula (IV).
A = OR;
X = H, or
A + X = 5-10 membered optionally fused heterocyclyl, and
R = 1-6C alkyl, 3-6C cycloalkyl, phenyl or benzyl,
provided that if a ring N atom is present, it is optionally substituted by 3-trifluoromethyl-4-cyanophenyl.
ACTIVITY - Cytostatic.
No biological data available.
MECHANISM OF ACTION - Androgen inhibitor.
USE - Used as a non-steroidal antiandrogen agent used in the treatment of prostate cancer and other androgen dependent conditions.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B06-H; B07-H; B10-A10; B14-D02; B14-H01; B14-L06
TECH UPTX: 20040218
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: The reaction partner comprises Y-CH2-C(Me)(OX1)-COA1, L-CH2-C(Me)=CH2 or L-CH2-COMe.
A1 = OR or 3-trifluoromethyl-4-cyanophenylamino;
Y = a leaving group;
X1 = H, or
X1 + Y = 3-6 membered heterocyclyl, or
X1 + A1 = 5- or 6-membered heterocyclyl, and
L = halo.
(II) Is reacted with Y1-CH2-C(Me)(OX2)-COA2 to form a compound of formula (IVA).
Y1 = a leaving group;
A2 = OR or 3-trifluoromethyl-4-cyanophenylamino, and
X2 = H, or
X2 + Y1 = 3-6 membered heterocyclyl, or
X2 + A2 = 5-10 membered optionally fused heterocyclyl,
Provided that if a ring N atom is present, it is optionally substituted by 3-trifluoromethyl-4-cyanophenyl.
Reaction of (II) with a reaction partner is effected in a biphasic reaction system or in a lower alcohol. A2 is 3-trifluoromethyl-4-cyanophenylamino and (IVA) is (I). Y1-CH2-C(Me)(OX2)-COA2 is optically active and (I) is enriched R-(I). (I) Is racemic and R-(I) isomer is isolated.
ABEX UPTX: 20040218
EXAMPLE - In a flask (25 ml) with a magnetic stirrer, N-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-3-iodo-2-methylpropanamide (0.200 g) and sodium p-fluorobenzenesulfinate (0.2 g) were dissolved in dimethylsulfoxide (3-4 ml) and heated at 60 degrees C for 18 hours. During the reaction, the next three portions of sodium p-fluorobenzenesulfinate (0.200 g) were added. The reaction was followed by high performance liquid

chromatography analysis. To the reaction mixture was added ethyl acetate (30 ml), brine (30 ml) and water (20 ml). The organic layer was washed with 0.5N aqueous HCl (20 ml), water (20 ml) and saturated aqueous NaHCO3 (20 ml). After drying (Na2SO4) and concentration in vacuo, the crude product was purified by column chromatography (Merck60 SiO2; eluent = ethyl acetate/heptane = 3/2) to give **bicalutamide** (0.050 g; 23%).

DEFINITIONS - Preferred Definitions:
Z = alkali metal, Mg halide or ammonium.

L106 ANSWER 7 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-012518 [01] WPIX
DNC C2004-003809
TI Pure **bicalutamide** preparation, useful as antiandrogen in treating prostate cancer, from epoxide or halohydrin (or their precursors) and p-fluorophenylsulfinate salt.
DC B05
IN BOR, A; LUKACS, F; OROSZ, G; SCHNEIDER, G; BOR, D; LUK CS, F
PA (HELM-N) HELM AG; (CFPH-N) CF PHARMA GYOGYSZERGYARTO KFT; (BORA-I) BOR A; (LUKA-I) LUKACS F; (OROS-I) OROSZ G; (SCHN-I) SCHNEIDER G
CYC 104
PI WO 2003097590 A1 20031127 (200401)* GE 26 C07C315-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
DE 10222104 A1 20031204 (200401) C07C315-00
AU 2003240634 A1 20031202 (200442) C07C315-00
US 2005033082 A1 20050210 (200512) C07C317-14
EP 1506170 A1 20050216 (200513) GE C07C315-00
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
ADT WO 2003097590 A1 WO 2003-EP4999 20030513; DE 10222104 A1 DE 2002-10222104 20020517; AU 2003240634 A1 AU 2003-240634 20030513; US 2005033082 A1 WO 2003-EP4999 20030513, US 2004-498862 20041008; EP 1506170 A1 EP 2003-730023 20030513, WO 2003-EP4999 20030513
FDT AU 2003240634 A1 Based on WO 2003097590; EP 1506170 A1 Based on WO 2003097590
PRAI DE 2002-10222104 20020517
IC ICM C07C315-00; C07C317-14
ICS C07C317-46
AB WO2003097590 A UPAB: 20040102
NOVELTY - Preparation of N-(4-cyano-3-trifluoromethyl-phenyl)-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methyl-propionamide (I) involves reacting N-(4-cyano-3-trifluoromethyl-2-methyl-oxirane-2-carboxamide or a corresponding halohydrin (or their precursors) with a p-fluorophenylsulfinate salt (IV) and if necessary converting the precursor residue.

DETAILED DESCRIPTION - Preparation of N-(4-cyano-3-trifluoromethyl-phenyl)-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methyl-propionamide of formula (I) involves reacting an epoxide of formula (II) or a halohydrin (or analog) of formula (III) with a p-fluorophenylsulfinate salt (IV) and if necessary converting a precursor group R into N-(4-cyano-3-trifluoromethyl-phenyl)-aminocarbonyl.

R = N-(4-cyano-3-trifluoromethyl-phenyl)-aminocarbonyl or its precursor;

X = leaving group.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - None given.

USE - (I) is an antiandrogen useful in the treatment of prostate carcinoma.

ADVANTAGE - Racemic or enantiomeric (I) is obtained in pharmaceutically acceptable purity by a simple and economical procedure, using (IV) as starting material (rather than the highly toxic p-fluorothiophenol plus expensive and/or dangerous oxidizing agents as in prior art methods).

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B10-A10; B14-D02A; B14-H01

TECH UPTX: 20040102

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: (II) is obtained from (III), conversion of (III) to (II) and reaction of (II) with (IV) preferably being carried out as a one-pot reaction. (II) or (III) is racemic or optically active R- or S-enantiomer form. (IV) is an alkali metal p-fluorophenylsulfinate, preferably the sodium salt.

ABEX UPTX: 20040102

SPECIFIC COMPOUNDS - (I) is specifically disclosed as **bicalutamide**.

EXAMPLE - A mixture of 7.0 g N-(4-cyano-3-trifluoromethyl-phenyl)-2-methyl-oxirane-2-carboxamide, 9.43 g sodium p-fluorophenylsulfinate, 50 ml methanol and 3 ml glacial acetic acid was heated under reflux for 5 hours, then evaporated. The residue was partitioned between dichloromethane and water, and the organic phase was washed, dried and evaporated. The residue was **recrystallized** from diisopropyl ether to give 7.1 g of **bicalutamide**, m.pt. 187-189 degrees C, purity 96.6% (by HPLC).

DEFINITIONS - Preferred Definitions:
R = N-(4-cyano-3-trifluoromethyl-phenyl)-aminocarbonyl or -CO-Y;
X = halo (e.g. Cl, Br or I) or alkyl- or arylsulfonate (e.g. mesylate, tosylate or brosylate).

L106 ANSWER 8 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2003-607903 [57] WPIX

DNC C2003-165631

TI Preparation of **bicalutamide** from N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline and monohypophthalic acid.

DC B05

IN ITAYA, N; KATSURA, T; SHINTAKU, T

PA (ITAY-I) ITAYA N; (KATS-I) KATSURA T; (SHIN-I) SHINTAKU T; (SUMO) SUMIKA FINE CHEM CO LTD

CYC 102

PI WO 2003053920 A1 20030703 (200357)* JA 46 C07C315-02
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2003191337 A1 20031009 (200367) C07C317-34
AU 2002354475 A1 20030709 (200428) C07C315-02
US 6740770 B2 20040525 (200435) C07C255-50
US 2004133031 A1 20040708 (200445) C07C317-26
EP 1462442 A1 20040929 (200463) EN C07C315-02
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
KR 2004063947 A 20040714 (200473) C07C315-02
BR 2002014933 A 20041214 (200510) C07C315-02

ADT WO 2003053920 A1 WO 2002-JP13058 20021213; US 2003191337 A1 WO 2002-JP13058 20021213, US 2003-362410 20030224; AU 2002354475 A1 AU

2002-354475 20021213; US 6740770 B2 WO 2002-JP13058 20021213, US 2003-362410 20030224; US 2004133031 A1 Div ex WO 2002-JP13058 20021213, Div ex US 2003-362410 20030224, US 2003-740140 20031218; EP 1462442 A1 EP 2002-788815 20021213, WO 2002-JP13058 20021213; KR 2004063947 A KR 2004-709014 20040611; BR 2002014933 A BR 2002-14933 20021213, WO 2002-JP13058 20021213

FDT AU 2002354475 A1 Based on WO 2003053920; US 6740770 B2 Based on WO 2003005392; EP 1462442 A1 Based on WO 2003053920; BR 2002014933 A Based on WO 2003053920

PRAI JP 2002-166213 20020606; JP 2001-380686 20011213

IC ICM C07C255-50; C07C315-02; C07C317-26; C07C317-34
ICS A61K031-277; A61K031-2777; A61P005-28; A61P005-288; A61P043-00; A61P043-000; C07C315-06; C07C315-066; C07C317-46; C07C317-466

AB WO2003053920 A UPAB: 20030906
NOVELTY - Preparation of **bicalutamide** (I) includes the step of reacting N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline (II) with monoperphthalic acid to give 4-cyano-N-(2,3-epoxy-2-methylpropionyl)-3-trifluoromethylaniline (III).

DETAILED DESCRIPTION - Preparation of **bicalutamide** of formula (I) includes the step of reacting N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline of formula (II) with monoperphthalic acid to give 4-cyano-N-(2,3-epoxy-2-methylpropionyl)-3-trifluoromethylaniline of formula (III).

INDEPENDENT CLAIMS are also included for:

(1) preparation of (I) which includes the step of reacting 4'-cyano-3-(4-fluorophenylthio)-2-hydroxy-2-methyl-3'-trifluoromethylpropionanilide of formula (IV) either with monoperphthalic acid or with hydrogen peroxide in the presence of a sodium tungstenate or its solvate, phenylsulfonic acid or a phase transfer catalyst in ethyl acetate;

(2) preparation of **crystalline** (I) comprising dissolving (I) in ethyl acetate, adding hexane, heptane or a similar hydrocarbon solvent, and **crystallizing** (I) from the solvent mixture; and

(3) **crystalline** (I) having 13C-NMR data given in the specification.

USE - For preparing **bicalutamide** preferably in **crystalline** form useful as an antiandrogenic agent.

ADVANTAGE - Processes are environmentally friendly, economical, efficient and safe.

Dwg.0/1

FS CPI

FA AB; GI; DCN

MC CPI: B05-A01B; B05-A03B; B07-A03; B10-A10; B10-A15; B14-D02

TECH UPTX: 20030906
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: (IV) Is oxidized is using 3-6 moles hydrogen peroxide per mole of (IV) in the presence of 0.5-5 moles of catalyst.

ABEX UPTX: 20030906
EXAMPLE - Monoperphthalic acid (108.05 g, then 19.82 g) was added to N-methacroyl-4-cyano-2-methylpropionyl)-3-trifluoromethaneaniline (II) (13.8 g) in ethyl acetate at 50-55 degrees C and the mixture was stirred at 50-55 degrees C for 3.9 hours. Monoperphthalic acid (10.36 g, then 1.90 g) was added and the mixture was reacted for a further hour. Work-up gave 4-cyano-N-(2,3-epoxy-2-methylpropionyl)-3-trifluoromethylaniline (III) (11.37 g; 77.3 % yield; 98.7 % purity).

L106 ANSWER 9 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2003-607707 [57] WPIX

DNC C2003-165435

TI Pharmaceutical product for treating prostate cancer comprises 4'-cyano-alpha,alpha,alpha-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-meta-toluidine in a solid dispersion containing an enteric polymer.

DC A96 B05
IN BATEMAN, N F; CAHILL, J K; CARMAN, N H; COCKSHOTT, I D; BATEMAN, N
PA (ASTR) ASTRAZENECA AB; (ASTR) ASTRAZENECA UK LTD
CYC 103
PI WO 2003043606 A1 20030530 (200357)* EN 28 A61K009-16 <--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2002343024 A1 20030610 (200419) A61K009-16 <--
EP 1448168 A1 20040825 (200456) EN A61K009-16 <--
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
BR 2002014135 A 20041013 (200477) A61K009-16 <--
US 2005038111 A1 20050217 (200514) A61K031-277
NO 2004002502 A 20040809 (200515) A61K009-16 <--
ADT WO 2003043606 A1 WO 2002-GB5159 20021114; AU 2002343024 A1 AU 2002-343024 20021114; EP 1448168 A1 EP 2002-779684 20021114, WO 2002-GB5159 20021114; BR 2002014135 A BR 2002-14135 20021114, WO 2002-GB5159 20021114; US 2005038111 A1 WO 2002-GB5159 20021114, US 2004-495012 20041004; NO 2004002502 A WO 2002-GB5159 20021114, NO 2004-2502 20040615
FDT AU 2002343024 A1 Based on WO 2003043606; EP 1448168 A1 Based on WO 2003043606; BR 2002014135 A Based on WO 2003043606
PRAI SE 2001-3839 20011116
IC ICM **A61K009-16**; A61K031-277
ICS **A61K009-14**; A61K031-56; A61K031-566
AB WO2003043606 A UPAB: 20030906
NOVELTY - A pharmaceutical product comprises 4'-cyano- alpha ', alpha ', alpha '-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-meta-toluidine (I) or its salt or solvate, in a solid dispersion containing an enteric polymer, and optionally an anti-estrogen and/or an aromatase inhibitor. The polymer has a pKa of 3-6.

ACTIVITY - Cytostatic; Antiseborrheic; Dermatological; Depilatory; Gynecological; Cardiovascular-Gen.; Vasotropic. A test formulation containing **bicalutamide** (0.5 g) and HP-55S (RTM; hydroxypropyl methyl cellulose acetate phthalate) was administered to 6 fasted dogs (equivalent to 450 mg of the drug). The comparative formulation was conventional **bicalutamide** tablets of **CASODEX** (RTM).
Each of the oral dose was followed by 20 ml of water. Blood samples were taken pre-dose and post-dose at 1, 2, 8, 18, 30, 72, 96, 120, 144 and 168 hours. The samples were centrifuged at 3000 rpm for 15 minutes, plasma was removed and analyzed for **bicalutamide**. The Cpmax (micro g/ml), Tmax (hours) and area under curve (AUC) (micro g/hour/ml) of the test/comparative formulation was found to be 13/5, 30/30 and 1504/500, respectively.

MECHANISM OF ACTION - Androgen Antagonist.

USE - In the manufacture of a pharmaceutical product for treating or reducing the risk of prostate cancer, and the side effects gynecomastia, breast tenderness, hot flushes, impotence and reduction in libido (claimed). Also useful for the treatment of a non-malignant disease of the prostate gland (e.g. benign prostatic hyperplasia or hypertrophy), testotoxicosis, hirsutism and acne.

ADVANTAGE - The composition increases the bioavailability of (I), reduces its inter-patient variability and thus enables the reduction of daily doses of the drug as compared to that required to achieve the same level of bioavailability obtained with the conventional formulation. The reduction in the inter-patient variability of the plasma concentration of the drug increases the predictability of the treatment and uniformity of treatment in a patient population. The formulation further exhibits enhanced storage stability.

Dwg.0/9
FS CPI
FA AB; DCN
MC CPI: A12-V01; B01-B03; B04-C02A; B07-D13; B10-A10; B10-B03B; B14-C01; B14-D01A; B14-D02A; B14-D03; B14-N07; B14-N07A; B14-N17D
TECH UPTX: 20030906
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The anti-estrogen and/or aromatase inhibitor is in a solid dispersion with the enteric polymer. (I) And the anti-estrogen are in a ratio of 25-350:0.5-100, respectively. (I) And the aromatase inhibitor are in a ratio of 25-350:0.005-100, respectively. The weight ratio of (I):enteric polymer is 1:0.25-1:10. The solid dispersion comprises a wetting agent. Greater than 50 (preferably at least 99, particularly substantially 100) % of (I) is present in the form of R-enantiomer and at least 30 (preferably 99) % of (I) is in **amorphous** form.
Preferred Components: The anti-estrogen is tamoxifen or its salt or solvate. The aromatase inhibitor is anastrazole, letrozole, exemestane or their salt or solvate.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The enteric polymer is hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose acetate, hydroxypropyl methylcellulose succinate, a methacrylic acid copolymer, polyvinyl acetate phthalate, cellulose acetate phthalate, methylcellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), cellulose propionate phthalate, hydroxypropyl methylcellulose butyrate phthalate, hydroxypropyl cellulose acetate phthalate succinate, hydroxypropyl methylcellulose trimellitate, cellulose acetate trimellitate, methylcellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate and/or cellulose acetate isophthalate (preferably HPMCP grade HP-50 (RTM), HPMCP grade HP-55 (RTM), HPMCP grade HP-55S (RTM), HPMCAS grade AS-LF (RTM), HPMCAS grade AS-MF (RTM), HPMCAS grade AS-HF (RTM), HPMCAS grade AS-LG (RTM), HPMCAS grade AS-MG (RTM), HPMCAS grade AS-HG (RTM), methacrylic acid copolymer grade A or methacrylic acid copolymer grade B; especially HPMCP grade HP-55S (RTM), HPMCAS grade AS-LG (RTM) or methacrylic acid copolymer grade A; particularly HPMCP grade HP-55S (RTM)).
ABEX UPTX: 20030906
ADMINISTRATION - The product is administered in a dosage form containing: (I) (25-1000 mg) and the anti-estrogen (0.5-200 mg) or aromatase inhibitor (0.005-200 mg) (claimed). Administration is mucosally, by inhalation, orally, intranasally or rectally, in 1-3 doses per day.

EXAMPLE - **Bicalutamide** (0.908 g) and tamoxifen citrate (0.092 g) were weighed in a round bottom flask, HP-55S (RTM; hydroxypropyl methyl cellulose acetate phthalate) (3 g) was added to the flask and dissolved in acetone (120 ml). The solvent was removed on the rotary evaporator, the formulation was placed in a vacuum oven and dried under high vacuum at 40 degrees C for 24 hours. The formulation was then retrieved from the flask and dry milled (350 rpm/15 minutes) and dried for further 24 hours under high vacuum at 40 degrees C.

L106 ANSWER 10 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-541456 [51] WPIX
DNC C2003-146865
TI Pharmaceutical product used for treating prostate cancer comprises 4'-cyano-alpha,alpha,alpha-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-meta-toluidine in solid dispersion containing polyvinyl

pyrrolidone.
DC A96 B05
IN BATEMAN, N F; CAHILL, J K; CARMAN, N H; COCKSHOTT, I D
PA (ASTR) ASTRAZENECA AB; (ASTR) ASTRAZENECA UK LTD
CYC 102
PI WO 2003043630 A1 20030530 (200351)* EN 21 A61K031-277
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2002339169 A1 20030610 (200419) A61K031-277
ADT WO 2003043630 A1 WO 2002-GB5158 20021114; AU 2002339169 A1 AU 2002-339169 20021114
FDT AU 2002339169 A1 Based on WO 2003043630
PRAI SE 2001-3838 20011116
IC ICM A61K031-277
ICS **A61K009-14**; A61K009-144; A61P035-00; A61P035-000
AB WO2003043630 A UPAB: 20030808
NOVELTY - Pharmaceutical product comprises 4'-cyano- alpha ', alpha ', alpha '-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-meta-toluidine (I) or its salt or solvate, in a solid dispersion containing polyvinyl pyrrolidone (PVP), and optionally an anti-estrogen and/or an aromatase inhibitor.

ACTIVITY - Cytostatic; Antiseborrheic; Dermatological; Depilatory; Gynecological; Vasotropic.

No biological tests or results are given.

MECHANISM OF ACTION - Androgen antagonist; Testosterone production inducer; Estrogen Antogonist.

USE - Used for treating or reducing the risk of prostate cancer, and the side effects gynaecomastia, breast tenderness, hot flushes, impotence and reduction in libido (claimed). The product is useful for the treatment of a non-malignant disease of the prostate gland (e.g. benign prostatic hyperplasia or hypertrophy), testotoxicosis, hirsutism and acne.

ADVANTAGE - The composition increases the bioavailability of (I), reduces its inter-patient variability and allows reduction of daily doses of the drug as compared to that required to achieve the same level of bioavailability obtained with the conventional formulation. The reduction in the inter-patient variability of the plasma concentration of the drug increases the predictability of the treatment and uniformity of treatment in a patient population. The product has improved storage stability.

Dwg.0/4
FS CPI
FA AB; DCN
MC CPI: A04-D05A; A12-V01; B01-B03; B04-C03A; B07-D03; B07-D13; B10-A10; B10-B03B; B14-C01; B14-D02A; B14-D05D; B14-F02; B14-H01; B14-N17
TECH UPTX: 20030808
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The antiestrogen and/or aromatase inhibitor is in a solid dispersion with PVP (preferably PVP K-25). (I) and the antiestrogen are in a ratio of 25-350:0.5-100, respectively. (I) And the aromatase inhibitor are in a ratio of 25-350:0.005-100, respectively. The weight ratio of (I):PVP is 1:0.25-1:10 (preferably 1:0.25-1: upto 3). The solid dispersion comprises a wetting agent. Greater than 50 (preferably at least 70, especially at least 99, particularly 100)% of (I) is in the form of the R-enantiomer and at least 30 (preferably 75, especially 95, particularly 99)% of (I) is in **amorphous** form.

Preferred Components: The anti-estrogen is tamoxifen or its salts or solvates. The aromatase inhibitor is anastrazole, letrozole, exemestane or their salts or solvates.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: PVP has a K value of upto 90.

ABEX UPTX: 20030808

ADMINISTRATION - The product is administered in a dosage form containing (in mg): 25-1000 (I) and 0.5-200 anti-estrogen or 0.005-200 aromatase inhibitor (claimed). Administration is mucosal, by inhalation, oral, intranasal or rectal, once a day or in 1-3 multiple doses.

EXAMPLE - **Bicalutamide** (0.5 g) and PVP K 25 (polyvinylpyrrolidone) (2.5 g) were dissolved in a mixture of acetone:dichloromethane (3:1) (80 ml). The solvent was removed on a rotary evaporator by spray drying, and the formulation was placed in a vacuum oven and dried under high vacuum at 40 degrees C for 24 hours. The formulation was then retrieved from the flask, dry milled and then dried for a further 24 hours under high vacuum at 40 degrees C. A comparative formulation was prepared similarly using the polymer PLA:PEG (2kDa, 2kDa) (a di-block copolymer of poly(lactide):polyethylene glycol) instead of PVP K 25. The formulations were weighed into hard gelatin capsules (equivalent to 50 mg of the drug) and dissolved in a media (containing 0.25% sodium dodecyl sulfate solution) (900 ml) for 1 hour at 37 degrees C. The samples (5 ml) were then removed at 5, 10, 20, 30, 45 and 60 minutes, centrifuged for 15 minutes and then analyzed by HPLC.

The cumulative release (in %) of **bicalutamide** in the test/comparative/control formulations at time (minutes) 20, 30, 40 and 60 was found to be 85/2/20, 97/5/24, 92/22/22 and 89/20/19 respectively. The test formulation exhibited 100% of **bicalutamide** in solution with the PVP K 25 and the supersaturation was maintained over 60 minutes test i.e. without the drug precipitation.

L106 ANSWER 11 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2003-523157 [49] WPIX

DNC C2003-140754

TI Preparation of solid dispersion comprises dissolving water insoluble drug and substituted cyclodextrin in organic solvent followed by drying.

DC B05 B07

IN JANG, S Y; SONG, J S; CHANG, S; SONG, J

PA (DDST-N) DDS TECH CO LTD

CYC 102

PI WO 2003043602 A1 20030530 (200349)* EN 15 A61K009-14 <--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
KR 2003041577 A 20030527 (200361) A61K009-14 <--
AU 2002366042 A1 20030610 (200419) A61K009-14 <--

ADT WO 2003043602 A1 WO 2002-KR2151 20021118; KR 2003041577 A KR 2001-72412 20011120; AU 2002366042 A1 AU 2002-366042 20021118

FDT AU 2002366042 A1 Based on WO 2003043602

PRAI KR 2001-72412 20011120

IC ICM **A61K009-14**

AB WO2003043602 A UPAB: 20030731

NOVELTY - Preparation of a solid dispersion comprising a water insoluble drug and a substituted cyclodextrin comprises dissolving the drug and the cyclodextrin in non-aqueous organic solvent followed by drying under reduced pressure or by spray drying.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a pharmaceutical composition which comprises the solid dispersion and a carrier.

ACTIVITY - None given

MECHANISM OF ACTION - None given.

USE - Used for manufacture of a solid dispersion (claimed).

ADVANTAGE - The method improves the dissolution rate and speed of water insoluble drugs, maximizes the bioavailability of the drug by promoting internal absorption and minimizes gastrointestinal side effects. The solid dispersion improves an individual's adaptability to the drugs producing side effects on the gastrointestinal tract when solubilized.
Dwg.0/6

FS CPI
FA AB; DCN
MC CPI: B01-B01; B01-B02; B01-B03; B01-C01; B01-C04; B01-C05; B04-C02B1; B05-B01G; B06-A03; B06-D09; B06-D17; B06-E01; B06-F01; B07-D02; B07-D03; B07-D05; B07-D10; B07-D13; B10-A04; B10-A08; B10-A09B
TECH UPTX: 20030731

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The water insoluble drug comprises at least one of ibuprofen, S-ibuprofen, ketoprofen, rofecoxib, celecoxib, indomethacin, piroxicam, nimesulide, diacerein, aceclofenac, nifedipine, nimodipine, felodipine, nitrendipine, isradipine, nisoldipine, nilvadipine, reserpine, acetazolamide, indapamide, furosemide, spironolactone, chlorthalidone, amrinone, milrinone, digitoxin, digoxin, itraconazole, saperconazole, amphotericin B, clotrimazole, griseofulvin, ketoconazole, miconazole, carbamazepine, oxcarbazepine, primidone, felbamate, lamotrigine, phenobarbital, phenytoin, alprazolam, estazolam, triazolam, risperidone, haloperidol, sulpiride, zotepine, thiothixene, chlorprothixene, clozapine, olanzapine, pimozide, diazepam, temazepam, oxazepam, lorazepam, clotiazepam, gliclazide, glimepiride, glipizide, glibenclamide, tolbutamide, pioglitazone hydrochloride, 9-aminocamptothecin, camptothecin, methotrexate, thioguanine, uracil mustard, tamoxifen citrate, carmustine, docetaxel, paclitaxel, danazol, chlorambucil, lomustine, etoposide, teniposide, busulfan, exemestane, 6-mercaptopurine, melphalan, flutamide, **bicalutamide**, megestrol acetate, progesterone, medroxyprogesterone acetate, altretamine, domperidone, levosulpiride, domperidone maleate, cisapride, S-omeprazole, omeprazole, lansoprazole, bisacodyl, sulfasalazine, acyclovir, ganciclovir, indinavir, nelfinavir, ritonavir, saquinavir, amprenavir, delavirdine, astemizole, loratadine, terfenadine, lovastatin, simvastatin, gemfibrozil, clofibrate, fenofibrate, probucol, dipyridamole, glyceryl trinitrate, amyl nitrate, isosorbide dinitrate, alprostadil, cyclosporins, tacrolimus, 8-methoxypsoralen, ursodesoxycholic acid, silymarin, biphenyldimethyldicarboxylate (DDB), alpha-lipoic acid, calcitriol, tretinoin, isotretinoin, folic acid, dl-alpha-tocopherol, dl-alpha-tocopherol acetate, lidocaine, benzocaine, testosterone, methyltestosterone, beclomethasone dipropionate, flunisolide, paramethasone, paramethasone acetate, prednisone, methyl prednisolone, methyl prednisolon acetonate, prednisolone, prednisolone acetate, dexamethasone, dexamethasone acetate, dexamethasone palmitate, cortisone, cortisone acetate, triamcinolone, triamcinolone acetonide, budesonide, fluticasone propionate, betamethasone, hydrocortisone, hydrocortisone acetate, fluorocortisone, fluorocortisone acetate, deflazacort, propofol, riluzole, bromocriptin mesylate, disulfiram, gamma-linoleic acid or sodium alendronate.
Preferred Composition: The solid dispersion comprises (in pts. wt.): substituted cyclodextrin (0.1-10) and the water insoluble drug (1).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The organic solvent comprises methanol, ethanol, isopropanol, propanol, acetone, ethyl acetate, methylethylketone, dimethylformamide (DMF), dichloromethane, chloroform, diethyl ether, dimethyl ether, tetrahydrofuran (THF), cyclohexane and/or dimethylsulfoxide (DMSO). The substituted cyclodextrin comprises at least one of 2,6-dimethyl-beta-cyclodextrin, 2-hydroxyethyl-beta-cyclodextrin, 2-hydroxyethyl-gamma-cyclodextrin, 2-hydroxypropyl-beta-cyclodextrin, 2-hydroxypropyl-gamma-cyclodextrin, (2carboxymethoxy)propyl-beta-cyclodextrin or sulfobutylether-7-beta-cyclodextrin.

ABEX UPTX: 20030731

ADMINISTRATION - Administration is oral, parenteral (e.g. intravenous, subcutaneous, intradermal, transdermal, transocular, transnasal, vaginal or anal) or by inspiration. No dosage is given.

EXAMPLE - A solid dispersion was prepared by mixing a solution of hydroxypropyl-beta-cyclodextrin (HP-beta-CD) dissolved in ethanol (200 ml) and a solution of ibuprofen (2 g) in dichloromethane (100 ml). The resultant mixture was stirred and dried under reduced pressure to obtain the dispersion.
The solid dispersion was tested for dissolution by a test as described in Korean Pharmacopoeia 7th revised version. The solid dispersion dissolved rapidly at pH 6.8. The dissolution rate (in %) was: 20 and 90 for ibuprofen alone and test, respectively. The results showed that the dissolution rate exceeded 90% as compared to ibuprofen powder.

L106 ANSWER 12 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-493136 [46] WPIX
DNC C2003-131939
TI New **bicalutamide** formulation with enhanced storage stability and bioavailability is a solid dispersion in an enteric polymer.
DC A11 A14 A96 B05 B07
IN BATEMAN, N F; CAHILL, J K
PA (ASTR) ASTRAZENECA AB; (ASTR) ASTRAZENECA UK LTD; (CAHI-I) CAHILL J K
CYC 102
PI WO 2003032950 A1 20030424 (200346)* EN 41 A61K009-14 <--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
JP 2004521963 W 20040722 (200448) 67 A61K031-277
EP 1439823 A1 20040728 (200449) EN A61K009-14 <--
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
AU 2002336169 A1 20030428 (200460) A61K009-14 <--
BR 2002013248 A 20040928 (200472) A61K009-14 <--
HU 2004001369 A2 20041129 (200503) A61K009-14 <--
NO 2004001485 A 20040413 (200508) A61K009-14 <--
JP 3639587 B2 20050420 (200527) 25 A61K031-277
ZA 2004002729 A 20050330 (200527) 50 A61K000-00
ADT WO 2003032950 A1 WO 2002-GB4621 20021011; JP 2004521963 W WO 2002-GB4621 20021011, JP 2003-535754 20021011; EP 1439823 A1 EP 2002-770069 20021011, WO 2002-GB4621 20021011; AU 2002336169 A1 AU 2002-336169 20021011; BR 2002013248 A BR 2002-13248 20021011, WO 2002-GB4621 20021011; HU 2004001369 A2 WO 2002-GB4621 20021011, HU 2004-1369 20021011; NO 2004001485 A WO 2002-GB4621 20021011, NO 2004-1485 20040413; JP 3639587 B2 WO 2002-GB4621 20021011, JP 2003-535754 20021011; ZA 2004002729 A ZA 2004-2729 20040407
FDT JP 2004521963 W Based on WO 2003032950; EP 1439823 A1 Based on WO 2003032950; AU 2002336169 A1 Based on WO 2003032950; BR 2002013248 A Based on WO 2003032950; HU 2004001369 A2 Based on WO 2003032950; JP 3639587 B2 Previous Publ. JP 2004521963, Based on WO 2003032950
PRAI SE 2001-3424 20011015
IC ICM A61K000-00; **A61K009-14**; A61K031-277
ICS A61K031-275; A61K035-00; A61K047-30; A61K047-32; A61K047-34; A61K047-38; A61P035-00
AB WO2003032950 A UPAB: 20030719
NOVELTY - A composition comprises 4'-cyano- alpha ', alpha ', alpha '-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide (**bicalutamide**) (more than 50% as the R-enantiomer) in a solid dispersion comprising an enteric polymer having a pKa of 3-6.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a solid dispersion of an enteric polymer (having a pKa of 3-6) with 4'-cyano- alpha ', alpha ', alpha '-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide;
(2) a method for treating prostate cancer comprising administration of the solid dispersion;
(3) a method for increasing the bioavailability of 4'-cyano- alpha ', alpha ', alpha '-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide comprising administration as the solid dispersion;
(4) a method for increasing the storage stability of 4'-cyano- alpha ', alpha ', alpha '-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide in solid dispersion comprising use of the R-enantiomer; and
(5) a method for preparing a formulation of 4'-cyano- alpha ', alpha ', alpha '-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide with reduced inter-patient variability in plasma concentration and/or increased bioavailability.
ACTIVITY - Cytostatic.
No biological data given.
MECHANISM OF ACTION - None given.
USE - The solid dispersion is useful for treating prostate cancer (claimed).
ADVANTAGE - The formulation has enhanced storage stability and bioavailability.
Dwg.0/6

FS CPI
FA AB; DCN
MC CPI: A03-A04A1; A12-V01; B04-C02A; B10-A10; B14-H01; B14-N07A
TECH UPTX: 20030719
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The enteric polymer is hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose acetate phthalate, hydroxypropylmethylcellulose acetate, hydroxypropylmethylcellulose succinate methacrylic acid copolymer, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), methylcellulose acetate phthalate, ethylcellulose acetate phthalate, hydroxypropylcellulose acetate phthalate, hydroxypropylmethylcellulose phthalate (HPMCP), cellulose propionate phthalate, hydroxypropylcellulose butyrate phthalate, hydroxypropylcellulose acetate phthalate succinate, hydroxypropylmethylcellulose trimellitate, cellulose acetate trimellitate (CAT), methylcellulose acetate trimellitate, ethylcellulose acetate trimellitate, hydroxypropylcellulose acetate trimellitate, hydroxypropylmethylcellulose acetate trimellitate, hydroxypropylcellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate and/or cellulose acetate isophthalate, especially HP-55S. The ratio of toluidide:polymer is 4:1-1:10 and the toluidide is preferably as the R-enantiomer. The solid dispersion may include a wetting agent.
ABEX UPTX: 20030719
ADMINISTRATION - A unit dose comprises 5-1000 mg **bicalutamide** (claimed).

EXAMPLE - 4'-Cyano-alpha',alpha',alpha'-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide (0.5 g) and polymer (2.5 g) were dissolved in acetone (60 ml) and CH2Cl2 (20 ml) and concentrated. The residual formulation was dried at 40 degrees C under high vacuum for 24 hours. The novel formulation gave a Cpmax of 13 microgram/ml compared to 5 microgram/ml for a conventional formulation, a Tmax of 30 hours (same as conventional formulation) and AUC of 1500 microgram/hour/ml compared to 500 microgram/hour/ml for the conventional formulation.

L106 ANSWER 13 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-468366 [44] WPIX
DNC C2003-124936
TI Use of a granule material based on pyrogenically produced silicon dioxide in a pharmaceutical composition or adsorbate.
DC B05 B07
IN HASENZAHL, S; HEYM, J; MEYER, J
PA (DEGS) DEGUSSA AG; (HASE-I) HASENZAHL S; (HEYM-I) HEYM J; (MEYE-I) MEYER J
CYC 101
PI WO 2003037379 A1 20030508 (200344)* EN 24 A61K047-02
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
DE 10153078 A1 20030522 (200344) A61K009-16 <--
US 2004022844 A1 20040205 (200411) A61K009-48 <--
EP 1439858 A1 20040728 (200449) EN A61K047-02
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
AU 2002321191 A1 20030512 (200464) A61K047-02
JP 2005508977 W 20050407 (200524) 31 A61K047-04
ADT WO 2003037379 A1 WO 2002-EP7588 20020706; DE 10153078 A1 DE 2001-10153078 20011030; US 2004022844 A1 Provisional US 2001-331533P 20011119, US 2002-281223 20021028; EP 1439858 A1 EP 2002-754850 20020706, WO 2002-EP7588 20020706; AU 2002321191 A1 AU 2002-321191 20020706; JP 2005508977 W WO 2002-EP7588 20020706, JP 2003-539719 20020706
FDT EP 1439858 A1 Based on WO 2003037379; AU 2002321191 A1 Based on WO 2003037379; JP 2005508977 W Based on WO 2003037379
PRAI DE 2001-10153078 20011030
IC ICM **A61K009-16**; **A61K009-48**; A61K047-02; A61K047-04
ICS A61K009-02; A61K009-06; A61K009-10; **A61K009-14**; A61K009-18; A61K009-20; A61K031-00; A61K031-165; A61K031-167; A61K031-355; A61K031-60; A61K031-616; A61K033-00; A61P029-00; A61P039-06; A61P043-00
AB WO2003037379 A UPAB: 20030710
NOVELTY - Use of granule material based on pyrogenically produced silicon dioxide in a pharmaceutical composition.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) A pharmaceutical composition comprising the granular material based on pyrogenically produced silicon dioxide and at least one pharmaceutical active constituent;
(2) An adsorbate of the granule material and at least one pharmaceutical active constituent or auxiliary substance; and
(3) Preparation of the adsorbate, involving:
(a) melting the substance(s) (preferably active constituent or auxiliary substance, or their distribution in the solvent) to be adsorbed;
(b) mixing the granular material with the resulting mixture; and
(c) optionally removing the solvent.
USE - The granular material is used in pharmaceutical composition or adsorbate (claimed).
The material is also used as carriers of pharmaceutical active constituents and/or an auxiliary substance.
ADVANTAGE - The granular material has higher bulk density and tamped density, improved flowability, narrower grain size distribution, and dust-free processing. The tablet form has higher mechanical stability and an improved disintegration behavior.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B01-B02; B02-A; B02-C; B04-A04; B04-B03A; B04-G21; B04-L01; B04-N02; B04-N02A; B05-A03B; B05-B01G; B05-B01P; B05-B02C; B06-H; B07-H;

B10-A10; B10-A13D; B10-A19; B10-B01A; B10-B02D; B10-B02F; B10-B03B; B10-B04B; B10-C02; B10-C03; B10-D03; B10-E04A; B10-E04B; B10-F02; B10-J02; B11-C09; B12-M05; B14-A01; B14-A02; B14-A04; B14-C01; B14-C03; B14-C06; B14-C08; B14-E07; B14-E08; B14-F01; B14-F02B; B14-F02F2; B14-F04; B14-F07; B14-F08; B14-G01; B14-H01; B14-J01; B14-J02; B14-J07; B14-K01; B14-L09; B14-N11; B14-N17C; B14-S04; B14-S09

TECH UPTX: 20030710

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The composition further comprises at least one pharmaceutical auxiliary substance.

The composition is in the form of a suspension, emulsion, aerosol, ointment, cream, gel, paste, suppository, stick, powder, topical powder, granular material, tablet, pastille, sugar-coated pill, film-coated tablet, hard gelatin capsule, soft gelatin capsule, extrudate, microcapsule or microsphere. Preferred Components: The granular material has a mean diameter of 10 - 120 mum and a BET surface of 40-400 m2/g (determination according to DIN 66 131 using N).

The pharmaceutical active constituent is, e.g. alpha-proteinase inhibitor, abacavir, abciximab, acarbose, acetylsalicylic acid, acyclovir, adenosine, albuterol, aldesleukin, alendronate, alfuzosin, alosetrone, alprazolam, alteplase, ambroxol, amifostine, amiodarone, amisulprid, amlodipine, or ancrod.

The pharmaceutical auxiliary substance is an antioxidant, binder, emulsifier, coloring agent, film-forming agent, filler, gel-forming agent, odoriferous substance, flavoring substance, preservative, solvent, oil, powder base, ointment base, acid and salt for the formation, replenishment and production of pharmaceutical composition, lubricant, release agent, suppository base, suspension stabilizer, sweetening agent, effervescent gas, emollient or sugar substitute.

ABEX UPTX: 20030710

ADMINISTRATION - The granular material can be administered orally or topically. No dosage given.

EXAMPLE - Pyrogenically produced silicon dioxide AEROSIL 300 (RTM) (10 kg) (A) was dispersed in fully deionized water (100 kg). The suspensions that were formed were spray dried at 380 degrees C. The deposition of the finished product was carried out using a filter. The heat treatment of the spray-dried granular materials was carried out at 105 degrees C to produce a granular material based on pyrogenically produced silicon dioxide. The granular material obtained (30 g) was added to a solution of acetylsalicylic acid (60 g) in acetone (500 ml) and the resultant mixture was stirred for 2 hours at room temperature. The acetone was distilled off and the resultant solid was dried for 2 hours at 45 degrees C and then allowed to stand overnight. The product was screened through screen. Hard gelatin capsules were filled with the product. For a comparison, AEROSIL 300 (RTM) was used instead of (A). The test/comparative capsule had a bulk density (g/l) of 347/323, tamped density (g/l) of 454/410 and mean capsule weight (mg) of 232/224.

L106 ANSWER 14 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-092917 [08] WPIX
DNC C2003-023174
TI Formulation for mucosal administration of **bicalutamide**, especially for treatment of prostate cancer, containing solid dispersion of drug with polyvinyl pyrrolidone to improve bioavailability and stability.
DC A96 B05
IN BATEMAN, N F; CAHILL, J K; CAHILL, J
PA (ASTR) ASTRAZENECA AB; (BATE-I) BATEMAN N F; (CAHI-I) CAHILL J; (ASTR) ASTRAZENECA UK LTD
CYC 101
PI WO 2002080902 A1 20021017 (200308)* EN 32 A61K031-277

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

NO	2003004386	A	20031128	(200407)		A61K031-277	
EP	1381358	A1	20040121	(200410)	EN	A61K031-277	
	R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
HU	2003003454	A2	20040128	(200415)		A61K031-277	
SK	2003001203	A3	20040302	(200419)		A61K031-277	
KR	2003087048	A	20031112	(200420)		A61K031-277	
BR	2002008421	A	20040330	(200424)		A61K031-277	
AU	2002249387	A1	20021021	(200433)		A61K031-277	
US	2004138299	A1	20040715	(200447)		A61K031-277	
JP	2004525164	W	20040819	(200455)	52	A61K031-277	
CZ	2003002647	A3	20040915	(200462)		A61K031-277	
MX	2003008999	A1	20040201	(200473)		A61K031-277	
CN	1536993	A	20041013	(200508)		A61K031-277	

ADT WO 2002080902 A1 WO 2002-GB1439 20020327; NO 2003004386 A WO 2002-GB1439 20020327, NO 2003-4386 20031001; EP 1381358 A1 EP 2002-718317 20020327, WO 2002-GB1439 20020327; HU 2003003454 A2 WO 2002-GB1439 20020327, HU 2003-3454 20020327; SK 2003001203 A3 WO 2002-GB1439 20020327, SK 2003-1203 20020327; KR 2003087048 A KR 2003-712900 20031001; BR 2002008421 A BR 2002-8421 20020327, WO 2002-GB1439 20020327; AU 2002249387 A1 AU 2002-249387 20020327; US 2004138299 A1 WO 2002-GB1439 20020327, US 2004-473709 20040311; JP 2004525164 W JP 2002-578941 20020327, WO 2002-GB1439 20020327; CZ 2003002647 A3 WO 2002-GB1439 20020327, CZ 2003-2647 20020327; MX 2003008999 A1 WO 2002-GB1439 20020327, MX 2003-8999 20031002; CN 1536993 A CN 2002-807747 20020327

FDT EP 1381358 A1 Based on WO 2002080902; HU 2003003454 A2 Based on WO 2002080902; SK 2003001203 A3 Based on WO 2002080902; BR 2002008421 A Based on WO 2002080902; AU 2002249387 A1 Based on WO 2002080902; JP 2004525164 W Based on WO 2002080902; CZ 2003002647 A3 Based on WO 2002080902; MX 2003008999 A1 Based on WO 2002080902

PRAI SE 2001-3565 20011025; SE 2001-1171 20010402; SE 2001-2957 20010904

IC ICM A61K031-277
ICS A61K009-10; **A61K009-14**; A61K047-32; A61P035-00

AB WO 200280902 A UPAB: 20030204

NOVELTY - A pharmaceutical formulation (A) for mucosal administration comprises 4'-cyano- alpha ', alpha ', alpha '-trifluoro-3-(4-phenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide (I) in a solid dispersion with polyvinyl pyrrolidone (PVP).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) solid (I)/PVP dispersions for use as medicaments;

(2) a method of enhancing storage stability of formulations containing (I);

(3) a method for increasing the bioavailability of formulations containing (I); and

(4) a method of reducing inter-patient variability in plasma concentrations of (I).

ACTIVITY - Cytostatic; Antiseborrheic; Dermatological.

MECHANISM OF ACTION - None given.

USE - (I), i.e. **bicalutamide**, is a non-steroidal antiandrogen, the (R)-enantiomer being the active form in vivo. (A) Is especially used for treating or preventing prostate cancer (claimed). Other possible uses are treatment of non-malignant diseases of the prostate (e.g. benign prostatic hyperplasia or hypertrophy) or acne.

ADVANTAGE - The use of PVP in a solid dispersion with (I) increases bioavailability, reduces the inter-patient variation in plasma levels and

improves the storage stability of (I) in the formulation. The increased bioavailability allows (I) to be used at reduced dioses and may also allow (I) to be used to treat more advanced forms of prostate cancer.
Dwg.0/4

FS CPI
FA AB; DCN
MC CPI: A04-D05A; A12-V01; B10-A10; B14-H01; B14-N07A; B14-N17C
TECH UPTX: 20030204
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: At least 50 % (preferably 100 %) of (I) is in (R)-enantiomer form; and at least 20 % of (I) is in amorphous form. The weight ratio of (I) to PVP is 1:0.25-10 (preferably 1:3-10). (A) Also contains a wetting agent. The PVP has a K-value of 90 or less (especially 25).
ABEX UPTX: 20030204
ADMINISTRATION - Administration of (I) is 10-1500 mg/day (claimed) orally (preferred; e.g. as a tablet), rectally, intranasally or by inhalation.

EXAMPLE - **Bicalutamide** (3.0 g) and polyvinyl pyrrolidone (PVP; 9.0 g) K-25 were dissolved under stirring in acetone/dichloromethane (3:1; 400 ml). The solution was spray-dried to give a free-flowing white powder. The powder (50 mg as (I)) was filled into a hard gelatin capsule and dissolved in 0.25 % sodium dodecyl sulfate solution (900 ml) for 1 hour at 37 degrees C under stirring at 75 rpm. 100 % of (I) was dissolved and supersaturation was maintained over the 60 minutes test (i.e. no precipitation of (I) was observed.

L106 ANSWER 15 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-067352 [06] WPIX
DNC C2003-017497
TI Mucosal **bicalutamide** formulation in solid dispersion with enteric polymer used for treating prostate cancer.
DC A11 A14 A96 B05 B07
IN CAHILL, J; FIELES, W E; BATEMAN, N
PA (ASTR) ASTRAZENECA AB; (BATE-I) BATEMAN N; (CAHI-I) CAHILL J; (ASTR) ASTRAZENECA UK LTD
CYC 101
PI WO 2002067893 A2 20020906 (200306)* EN 26 A61K009-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
GB 2372444 A 20020828 (200306) A61K047-38
NO 2003003785 A 20031024 (200377) A61K009-19
CZ 2003002225 A3 20031112 (200379) A61K031-167
EP 1368001 A2 20031210 (200382) EN A61K009-16 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2003077042 A 20030929 (200410) A61K047-30
HU 2003002847 A2 20031229 (200413) A61K009-16 <--
SK 2003001072 A3 20040203 (200413) A61K009-00
US 2004067257 A1 20040408 (200426) A61K031-277
BR 2002007572 A 20040427 (200430) A61K009-00
AU 2002232012 A1 20020912 (200433) A61K009-00
JP 2004143185 A 20040520 (200434) 14 A61K031-277
JP 2004521918 W 20040722 (200448) 44 A61K031-167
JP 3548566 B2 20040728 (200449) 14 A61K031-167
CN 1503662 A 20040609 (200460) A61K009-16 <--
MX 2003007641 A1 20040101 (200471) A61K009-00
NZ 527532 A 20041224 (200506) A61K009-00
ZA 2003006383 A 20050126 (200513) 35 A61K000-00

ADT WO 2002067893 A2 WO 2002-GB766 20020222; GB 2372444 A GB 2001-4749 20010227; NO 2003003785 A WO 2002-GB766 20020222, NO 2003-3785 20030826; CZ 2003002225 A3 WO 2002-GB766 20020222, CZ 2003-2225 20020222; EP 1368001 A2 EP 2002-712105 20020222, WO 2002-GB766 20020222; KR 2003077042 A KR 2003-711178 20030826; HU 2003002847 A2 WO 2002-GB766 20020222, HU 2003-2847 20020222; SK 2003001072 A3 WO 2002-GB766 20020222, SK 2003-1072 20020222; US 2004067257 A1 WO 2002-GB766 20020222, US 2003-468276 20030818; BR 2002007572 A BR 2002-7572 20020222, WO 2002-GB766 20020222; AU 2002232012 A1 AU 2002-232012 20020222; JP 2004143185 A Div ex JP 2002-567261 20020222, JP 2004-41583 20040218; JP 2004521918 W JP 2002-567261 20020222, WO 2002-GB766 20020222; JP 3548566 B2 JP 2002-567261 20020222, WO 2002-GB766 20020222; CN 1503662 A CN 2002-808735 20020222; MX 2003007641 A1 WO 2002-GB766 20020222, MX 2003-7641 20030826; NZ 527532 A NZ 2002-527532 20020222, WO 2002-GB766 20020222; ZA 2003006383 A ZA 2003-6383 20030815

FDT CZ 2003002225 A3 Based on WO 2002067893; EP 1368001 A2 Based on WO 2002067893; HU 2003002847 A2 Based on WO 2002067893; SK 2003001072 A3 Based on WO 2002067893; BR 2002007572 A Based on WO 2002067893; AU 2002232012 A1 Based on WO 2002067893; JP 2004521918 W Based on WO 2002067893; JP 3548566 B2 Previous Publ. JP 2004521918, Based on WO 2002067893; MX 2003007641 A1 Based on WO 2002067893; NZ 527532 A Based on WO 2002067893

PRAI SE 2001-2572 20010719; GB 2001-4749 20010227

IC ICM A61K000-00; A61K009-00; **A61K009-16**; A61K009-19; A61K031-167; A61K031-277; A61K047-30; A61K047-38

ICS **A61K009-14**; A61K009-20; A61K009-24; A61K009-32; A61K009-36; A61K031-56; A61K047-32; A61P005-28; A61P013-08; A61P035-00; A61P035-04

AB WO 200267893 A UPAB: 20030124

NOVELTY - Mucosal formulation comprises **bicalutamide** (I) in solid dispersion with an enteric polymer (II) having a pKa of 3-6.

ACTIVITY - Cytostatic; Antiseborrheic; Dermatological.

In a test, oral doses of a 1:3 (I):HP-55S solid dispersion (equivalent to 450 mg (I)) were administered to fasted dogs followed by 20 ml water. The Cpmax was 13 micro g/ml, the Tmax was 30 hours and the AUC was 1504 mu g/h/ml, compared with 5 mu g/ml, 30 hours and 500 mu g/h/ml respectively for conventional **Casodex** tablet formulations.

MECHANISM OF ACTION - None given in the source material.

USE - Used for treating and/or reducing the risk of prostate cancer. (I) is also useful for treatment of non-malignant disease of the prostate gland e.g. benign prostatic hyperplasia or hypertrophy and acne.

ADVANTAGE - The use of the polymer increases the bioavailability of (I) and reduces inter-patient variability in plasma concentrations of (I). The increase in bioavailability of (I) enables a reduction in dosage and may permit the use of (I) to be extended to more advanced stages of prostate cancer than prior art compositions.

Dwg.0/4

FS CPI

FA AB; DCN

MC CPI: A12-V01; B04-C02A; B10-A10; B14-H01; B14-N07A; B14-N17D

TECH UPTX: 20030124

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The enteric polymer comprises hydroxypropyl methylcellulose acetate (HPMC) succinate, HPMC acetate phthalate, HPMC acetate, HPMC succinate, a methacrylic acid copolymer, polyvinyl acetate phthalate, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, HPMC phthalate, hydroxypropyl cellulose acetate phthalate succinate, HPMC trimellitate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, HPMC acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate or cellulose

acetate isophthalate.
The enteric polymer preferably comprises HPMC phthalate grade HP-50, HP-55 or HP-55S, HPMC succinate grade AS-LF, AS-MF, AS-HF, AS-LG, AS-MG or AS-HG or methacrylic acid copolymer grade A or B, especially HPMC phthalate grade HP-55S, HPMC succinate grade AS-LG or methacrylic acid copolymer grade A.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: The weight ratio of (I):(II) is 1:0.25-1:10. The solid dispersion comprises a wetting agent.

ABEX UPTX: 20030124
ADMINISTRATION - The dosage of (I) is 25-1000 mg/day by inhalation, intranasally, rectally or orally.

L106 ANSWER 16 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2002-691581 [74] WPIX
CR 2002-698571 [75]
DNC C2002-195428
TI Solid dispersion formulation useful in the treatment of e.g. cardiovascular disease comprises an active drug substance, at least one hydrophobic matrix former and at least one hydrophilic matrix former.
DC A96 B07
IN JUPPO, A M; JUPPO, A
PA (ASTR) ASTRAZENECA AB; (JUPP-I) JUPPO A
CYC 101
PI WO 2002064121 A1 20020822 (200274)* EN 31 A61K009-22
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
NO 2003003564 A 20031002 (200373) A61K009-22
EP 1368006 A1 20031210 (200382) EN A61K009-22
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
BR 2002006825 A 20040225 (200416) A61K009-22
US 2004067256 A1 20040408 (200425) A61K009-24
AU 2002228579 A1 20020828 (200427) A61K009-22
JP 2004518709 W 20040624 (200442) 45 A61K045-00
CN 1491104 A 20040421 (200446) A61K009-16 <--
CN 1491105 A 20040421 (200446) A61K009-22
MX 2003007092 A1 20031201 (200470) A61K047-30
KR 2004058103 A 20040703 (200472) A61K009-22
NZ 526994 A 20050128 (200513) A61K009-22
ADT WO 2002064121 A1 WO 2002-SE228 20020208; NO 2003003564 A WO 2002-SE228 20020208, NO 2003-3564 20030812; EP 1368006 A1 EP 2002-710645 20020208, WO 2002-SE228 20020208; BR 2002006825 A BR 2002-6825 20020208, WO 2002-SE228 20020208; US 2004067256 A1 WO 2002-SE228 20020208, US 2003-467900 20030811; AU 2002228579 A1 AU 2002-228579 20020208; JP 2004518709 W JP 2002-563916 20020208, WO 2002-SE228 20020208; CN 1491104 A CN 2002-804914 20020208; CN 1491105 A CN 2002-804906 20020208; MX 2003007092 A1 WO 2002-SE228 20020208, MX 2003-7092 20030807; KR 2004058103 A KR 2003-710577 20030812; NZ 526994 A NZ 2002-526994 20020208, WO 2002-SE228 20020208
FDT EP 1368006 A1 Based on WO 2002064121; BR 2002006825 A Based on WO 2002064121; AU 2002228579 A1 Based on WO 2002064121; JP 2004518709 W Based on WO 2002064121; MX 2003007092 A1 Based on WO 2002064121; NZ 526994 A Based on WO 2002064121
PRAI SE 2001-478 20010213; SE 2001-477 20010213
IC ICM **A61K009-16**; A61K009-22; A61K009-24; A61K045-00; A61K047-30
ICS **A61K009-14**; A61K009-26; A61K009-52; A61K031-277; A61K031-4422; A61K047-00; A61K047-10; A61K047-12; A61K047-14;

A61K047-34; A61K047-38; A61K047-44; A61P001-04; A61P009-00; A61P009-08; A61P009-12; A61P035-00; C07D211-90

AB WO 200264121 A UPAB: 20050224

NOVELTY - A multiparticulate, modified release solid dispersion formulation comprises an active drug substance, at least one hydrophobic matrix former and at least one hydrophilic matrix former.

DETAILED DESCRIPTION - A multiparticulate, modified release solid dispersion formulation (I) comprises an active drug substance (a), at least one hydrophobic matrix former (b) and at least one hydrophilic matrix former (c). (a) has a water solubility of at most 8 mg/ml at room temperature. (b) is a meltable, non-swelling amphiphilic lipid having a water solubility of less than 1 mg/g. (c) is a meltable excipient having a water solubility more than 0.1 g/g. The weight ratio of (b):(c) is at least 1. The particle size of (I) is less than 300 micro m.

INDEPENDENT CLAIMS are also included for the following:

(1) preparation of (I) by spray congealing: and

(2) tablet comprising (I) and additionally at least one excipient.

ACTIVITY - Cytostatic; Hypotensive; Cardiovascular-Gen.

MECHANISM OF ACTION - None given.

USE - In the manufacture of a medicament for the treatment of a cardiovascular disease and cancer therapy (claimed) e.g. hypertension, prostrate cancer.

ADVANTAGE - The formulation is a multiparticulate, modified release solid dispersion and has low solubility in water.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: A12-V01; B04-B01B; B04-C03; B10-C04E; B10-E04C; B10-G02; B14-F01; B14-F02B; B14-H01

TECH UPTX: 20021118

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (b) is a water insoluble, non-swelling fatty acid having a melting point above 50 (preferably 55 - 75) degreesC. (b) is stearic acid, palmitic acid, myristic acid, fatty acid ester (preferably glyceryl monostearate, glyceryl behenate, glyceryl dipalmitostearate or glyceryl di or tristearate), hydrogenated fatty acid ester (preferably hydrogenated castor oil), mixture of mono-triglycerides, and/or fatty alcohols (preferably cetyl alcohol, stearyl alcohol and/or cetostearyl alcohol). The excipient is sodium stearyl fumarate.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: (c) is polyethyleneoxide, polyethyleneoxide and polypropyleneoxide block-co-polymers, polaxamer (preferably polaxmer 407), and/or polyethylene glycol (preferably PEG 4000 or PEG 6000). (b) are polyethyleneglycol esters of fatty acids and/or waxes (e.g. carnauba wax). The excipient is **microcrystalline** cellulose.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Formulation: The total amount of (a) is less than 40 wt.% and is selected from felodipine or **bicalutamide.**

Preferred Method: The spray congealing involves:

(1) melting (b);

(2) dissolving or emulsifying (a) into the melt;

(3) dissolving (c) into the melt;

(4) atomizing the melt into droplets; and

(5) solidifying the droplets.

ABEX UPTX: 20021118

ADMINISTRATION - (I) is administered orally in the form of tablet in a unit dosage form (claimed).

EXAMPLE - Felodipine (1 g) was dissolved in a melt of cetanol (4 g) at 110 degreesC. PEG 4000 (polyethyleneglycol) (2 g) was added into the melt. The melted mixture was kept at 110degreesC and atomized at 400 degrees C and a

pressure of 7 bar. The particles were collected into a vessel kept on carbondioxide ice and dried over night in a vacuum oven at 25 degrees C and 2 mbar. The resulted particles had a 90 % fractile size (90 % smaller than) of 78 microns and roundness of 0.85.

L106 ANSWER 17 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2001-355089 [37] WPIX
DNC C2001-109964
TI Asymmetric synthesis of enantiomers of acylanalides and/or their intermediates, particularly **bicalutamide**, useful e.g. for treating prostate cancer.
DC B05
IN EKWURIBE, N N; EKWURIBE, N
PA (NOBE-N) NOBEX CORP; (EKWU-I) EKWURIBE N N
CYC 95
PI WO 2001028990 A2 20010426 (200137)* EN 44 C07C315-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001019686 A 20010430 (200148) C07C315-00
NO 2002001831 A 20020619 (200253) C07C315-00
EP 1222165 A2 20020717 (200254) EN C07C317-34
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2002001340 A3 20020814 (200263) C07C315-00
BR 2000014889 A 20021231 (200309) C07C315-00
KR 2002091047 A 20021205 (200324) C07C315-00
JP 2003512351 W 20030402 (200325) 53 C07C319-20
HU 2002003785 A2 20030428 (200337) C07C317-34
US 6583306 B1 20030624 (200343) C07C315-00
CN 1409702 A 20030409 (200345) C07C317-34
ZA 2002002947 A 20030923 (200368) 66 C07C000-00
US 2004030130 A1 20040212 (200412) C07D279-12
NZ 518392 A 20040227 (200418) C07C315-00
ADT WO 2001028990 A2 WO 2000-US41233 20001018; AU 2001019686 A AU 2001-19686 20001018; NO 2002001831 A WO 2000-US41233 20001018, NO 2002-1831 20020418; EP 1222165 A2 EP 2000-982690 20001018, WO 2000-US41233 20001018; CZ 2002001340 A3 WO 2000-US41233 20001018, CZ 2002-1340 20001018; BR 2000014889 A BR 2000-14889 20001018, WO 2000-US41233 20001018; KR 2002091047 A KR 2002-704966 20020418; JP 2003512351 W WO 2000-US41233 20001018, JP 2001-531790 20001018; HU 2002003785 A2 WO 2000-US41233 20001018, HU 2002-3785 20001018; US 6583306 B1 Provisional US 1999-160412P 19991019, US 2000-691621 20001018; CN 1409702 A CN 2000-817022 20001018; ZA 2002002947 A ZA 2002-2947 20020415; US 2004030130 A1 Provisional US 1999-160412P 19991019, Div ex US 2000-691621 20001018, US 2003-444343 20030523; NZ 518392 A NZ 2000-518392 20001018, WO 2000-US41233 20001018
FDT AU 2001019686 A Based on WO 2001028990; EP 1222165 A2 Based on WO 2001028990; CZ 2002001340 A3 Based on WO 2001028990; BR 2000014889 A Based on WO 2001028990; JP 2003512351 W Based on WO 2001028990; HU 2002003785 A2 Based on WO 2001028990; US 2004030130 A1 Div ex US 6583306; NZ 518392 A Based on WO 2001028990
PRAI US 1999-160412P 19991019; US 2000-691621 20001018; US 2003-444343 20030523
IC ICM C07C000-00; C07C315-00; C07C317-34; C07C319-20; C07D279-12
ICS C07C231-00; C07C255-49; C07C315-02; C07C317-14; C07C317-46; C07C319-14; C07C323-52; C07C323-60; C07M007-00
ICA C07B053-00; C07D317-34; C07D498-04
ICI C07M007:00
AB WO 200128990 A UPAB: 20020226
NOVELTY - Enantiomers of acylanilides and/or their intermediates are

prepared with improved separation, and the preferred (R)-enantiomer of **bicalutamide** is prepared using (S) citramalic acid as a starting material.

DETAILED DESCRIPTION - Asymmetric synthesis of an enantiomer of an acylanilide, or a derivative, comprises: (a) contacting a compound having a ring structure that, when opened, provides a substituent having the structure (I), with a compound of formula R7-R6-X1-H (II) to give (III);

R1 = 1-4C alkyl or 1-4C haloalkyl;

R2 = 1-6C alkyl;

R3 = CH2OR4;

R4 = H, benzyl, C(O)Me or C(O)OR5;

R5 = H or alkyl;

R6 = a direct link or 1-6C alkyl;

R7 = 1-6C alkyl, 2-6C alkenyl, 1-6C hydroxyalkyl or 3-6C cycloalkyl; phenyl substituted with 1-3 Q; naphthyl; or Het;

Q = H, halo, NO2, carboxy, carbamoyl or CN; or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulfonyl, alkylsulfonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulfinyl, perfluoroalkylsulfonyl, alkoxycarbonyl or N-alkylcarbamoyl, each of 1-4C; or phenyl, phenylthio, phenylsulfinyl or phenylsulfonyl;

Het = a 5-6 membered optionally unsaturated heterocyclic containing 1-3 heteroatoms (O, N or S), which may be a single ring or fused to a benzo-ring; and the heterocyclic is optionally substituted with 1 or 2 halo, CN or NH2, or alkyl, alkoxy, alkylsulfinyl or alkylsulfonyl, each of 1-4C, or oxy or OH, or 1 or 2 oxo substituents;

X1 = O, S, -SO-, -SO2-, -NH- or -NR8-;

R8 = 1-6C alkyl;

X2 = as defined for X1 or -NR8a-;

R8a = oxidized alkylimino;

and (b) treating (III) under suitable conditions to give a pure enantiomer of an acylanilide or derivative.

INDEPENDENT CLAIMS are included for the following: (1) new intermediates of formula (IV) and their preparation;

R9 = H or straight, branched or cyclic alkyl;

R10 = alkyl, aryl or R11X43;

R11 = alkyl;

X4 = alkyl, halo or aryl;

X3 = a leaving group;

and (2) preparation of optically active compounds (III); (3) preparation of a pure enantiomer of an acylanilide or derivative of formula (XIVA) from citramalic acid by the following reaction scheme:

(i) aldol condensation with citramalic acid (X) to give (XV);

(ii) decarboxylating (XV) to give (IVA);

(iii) hydrolyzing (IVA) to give (XXIII);

(iv) treating (XXIII) with (II) to give (XVIII);

(v) treating (XVIII) with (XIII);

(vi) oxidizing the product from (v) to give (XIVA).

R14 = CN, carbamoyl, NO2, F, Cl, Br or I; or alkanoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulfinyl or perfluoroalkylsulfonyl each having 1-4C; or phenylthio, phenylsulfinyl or phenylsulfonyl;

R13 = R14, H, 1-4C alkyl or 1-4C alkoxy; and

R15 = H or halo.

ACTIVITY - Anticancer.

MECHANISM OF ACTION - None given

USE - The acylanilide bicalutamide (N-(4-cyano-3 (trifluoromethyl)phenyl)-3-((4-fluorophenyl)sulfonyl)-2-hydroxy-2 methyl-propanamide) (particularly R-enantiomer) is useful for treating androgen-dependent diseases, e.g. prostate cancer.

ADVANTAGE - The asymmetric methods are more cost effective than conventional methods, and do not require use of the expensive (R) proline as in previous methods.

Dwg.0/3

FS CPI
FA AB; GI; DCN
MC CPI: B10-D03; B14-H01
TECH UPTX: 20010704
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Methods: The compound having a ring structure is of formula (IV), (VIII) or (XI), and reacts with (II) to form (V), (IX) or (XII) respectively.
X5 = a leaving group.
Compound (V), (IX) or (XII) is reacted to form (III).
In step (b), (III) is treated with a compound of formula (XIII) to form acylanilide (XIV):
Preferred Preparation of (XIVA): Step (i) is carried out with bromal in the presence of sulfuric acid. In step (ii) decarboxylation is carried out by decarboxylatively brominating with 2-mercaptoyridine N-oxide, dicyclohexylcarbodiamide and CBrCl3. In step (iii) hydrolysis is carried out with HCl. In step (iv), (II) is 4-fluorobenzenethiol, and in step (v), (XVIII) is reacted with thionyl chloride to give the acid chloride, then reacted with 4-amino-2-trifluoromethylbenzonitrile. Oxidation in step (vi) is carried out with meta-chloroperbenzoic acid. (S) Citramalic acid produces (R)-**bicalutamide**, and (R)-citramalic acid produces the (S)-enantiomer.
ABEX UPTX: 20010704
SPECIFIC COMPOUNDS - 5-Bromomethyl-5-methyl-2-tribromomethyl (1,3)dioxolan-4-one (IVa) is specifically claimed.
EXAMPLE - Bromal (89.1 mmol) and (S)-citramalic acid (74.2 mmol) were cooled to 0degreesC under an inert atmosphere, and sulfuric acid (25 ml) was added dropwise with stirring. After 2 hours, cooling was removed and the mixture was stirred overnight at room temperature. The solution was diluted with ice and extracted repeatedly with ethyl acetate. The organic layer was back extracted with water, dried and filtered. The filtrate was concentrated, and **crystallization** from toluene/hexanes gave 4 methyl-5-oxo-2-tribromomethyl-(1,31-dioxolan-4-yl)-acetic acid (60% yield).
This compound and 2-mercaptopyridine N-oxide were suspended in CBrCl3, and refluxed. A solution of dicyclohexylcarbodiamide in CBrCl3 was added slowly over 30 minutes. After stirring for 1 hour, the product was purified by silica gel chromatography to give (IVa) (65% yield), m.pt. 110-113degreesC.
(IVa) was dissolved in a mixture of isopropanol:1M NaOH (1:1). After 3 hours, 4-fluorobenzenethiol was added, and the mixture was stirred overnight. pH was adjusted to 8 and the mixture was extracted with CH2Cl2. Work up and **recrystallization** from CHCl3/petroleum ether gave 3-(4-fluoro phenylsulfanyl)-2-hydroxy-2-methyl-propionic acid. (80% yield), m.pt. 73-75degreesC.
The hydroxyacid (8.5 mmol) and 4-amino-2 trifluoromethylbenzonitrile (11 mmol) were dissolved in dry dimethylacetamide (15 ml) under an inert atmosphere. The solution was cooled to -10degreesC, and thionyl chloride (10 mmol) was added slowly. The mixture was stirred for 15 minutes at -10degreesC, and overnight at room temperature, then diluted with CH2Cl2 and extracted with saturated NaHCO3. Work up and purification by silica gel chromatography gave N-(4-cyano-3-trifluoromethyl phenyl)-3-(4-fluoro-phenylsulfanyl)-2-hydroxy-2-methyl propionamide (45%).
This compound (3.19 mmol) was dissolved in CH2Cl2 (43 ml) and meta-chloroperbenzoic acid (9.57 mmol) was added. After stirring overnight at room temperature, the mixture was diluted with ethyl acetate and extracted with Na2SO3 and NaHCO3. Work up and purification by silica gel chromatography gave **bicalutamide** (94% yield), m.pt. 178degreesC.

L106 ANSWER 18 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2001-343585 [36] WPIX
DNC C2001-106402
TI Resolution of intermediates useful in synthesis of acylanilide compounds, e.g., the anticancer agent **bicalutamide**, especially by resolving

a cinchonidine salt by **crystallization.**

DC B05
IN EKWURIBE, N N; JAMES, K D; RAJAGOPALAN, J
PA (NOBE-N) NOBEX CORP
CYC 95
PI WO 2001034563 A1 20010517 (200136)* EN 27 C07C315-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001026195 A 20010606 (200152) C07C315-06
BR 2000015124 A 20020702 (200252) C07C315-06
NO 2002001999 A 20020620 (200253) C07C000-00
EP 1224167 A1 20020724 (200256) EN C07C315-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2002001434 A3 20021113 (200282) C07C315-06
KR 2002067509 A 20020822 (200310) C07C315-06
HU 2002003186 A2 20030128 (200323) C07C315-06
JP 2003513955 W 20030415 (200328) 30 C07B057-00
CN 1413188 A 20030423 (200347) C07C315-06
US 6593492 B1 20030715 (200348) C07C067-02
ZA 2002003228 A 20030923 (200368) 45 C07C000-00
MX 2002004225 A1 20021001 (200370) C07C315-06
NZ 518552 A 20031031 (200380) C07C315-06

ADT WO 2001034563 A1 WO 2000-US41609 20001025; AU 2001026195 A AU 2001-26195 20001025; BR 2000015124 A BR 2000-15124 20001025, WO 2000-US41609 20001025; NO 2002001999 A WO 2000-US41609 20001025, NO 2002-1999 20020426; EP 1224167 A1 EP 2000-989719 20001025, WO 2000-US41609 20001025; CZ 2002001434 A3 WO 2000-US41609 20001025, CZ 2002-1434 20001025; KR 2002067509 A KR 2002-705357 20020426; HU 2002003186 A2 WO 2000-US41609 20001025, HU 2002-3186 20001025; JP 2003513955 W WO 2000-US41609 20001025, JP 2001-536512 20001025; CN 1413188 A CN 2000-817760 20001025; US 6593492 B1 Provisional US 1999-161884P 19991027, US 2000-695884 20001025; ZA 2002003228 A ZA 2002-3228 20020423; MX 2002004225 A1 WO 2000-US41609 20001025, MX 2002-4225 20020426; NZ 518552 A NZ 2000-518552 20001025, WO 2000-US41609 20001025

FDT AU 2001026195 A Based on WO 2001034563; BR 2000015124 A Based on WO 2001034563; EP 1224167 A1 Based on WO 2001034563; CZ 2002001434 A3 Based on WO 2001034563; HU 2002003186 A2 Based on WO 2001034563; JP 2003513955 W Based on WO 2001034563; MX 2002004225 A1 Based on WO 2001034563; NZ 518552 A Based on WO 2001034563

PRAI US 1999-161884P 19991027; US 2000-695884 20001025

IC ICM C07B057-00; C07C000-00; C07C067-02; C07C315-06
ICS C07C315-04; C07C317-28; C07C317-46

AB WO 200134563 A UPAB: 20010628
NOVELTY - A pure enantiomer of an acylanilide is prepared by:
(a) resolving an intermediate (I); and
(b) treating the resolved intermediate (I) under conditions sufficient to give a pure enantiomer of an acylanilide.
DETAILED DESCRIPTION - Preparation of a pure enantiomer of an acylanilide comprises:
(a) resolving an intermediate compound of formula (I); and
(b) treating the resolved intermediate (I) under conditions sufficient to give a pure enantiomer of an acylanilide.
R1 = T' or 1-4C haloalkyl;
R2 = 1-6C alkylene;
R3 = 1-6C alkylene, or a bond;
R4 = 1-6C alkyl, 2-6C alkenyl, 1-6C hydroxyalkyl or 3-6C cycloalkyl; Ph (optionally substituted by 1-3 halo, NO2, carboxy, carbamoyl, CN, T', T'O, 1-4C alkanoyl, T'S, T'SO, T'SO2, Q, QS, QSO, QSO2, T'OOC, CONHT', Ph,

PhS, PhSO or PhSO2); naphthyl; or Het (optionally substituted by 1-2 halo, CN, amino, T', T'S, T'SO, T'SO2, oxy or hydroxy substituents, or (if sufficiently saturated) 1-2 oxo substituents);
X1 = O, S, SO, SO2, NH or NR5;
R5 = 1-6C alkyl;
T', Q = 1-4C alkyl and 1-4C perfluoroalkyl respectively;
Ph = phenyl; and
Het = a 5-6 membered saturated or unsaturated heterocycle which contains 1-3 O, N and/or S atoms and which is optionally fused to a benzo ring.
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - None given.
USE - The process is useful for production of pure enantiomers of acylanilide compounds, especially **bicalutamide**, which is useful in treatment of prostate cancer.
ADVANTAGE - The process allows resolution of enantiomers of intermediate compounds before reaction with expensive materials which introduce other portions to the final molecule. This means that these expensive materials are not used in production of inactive enantiomers which will be discarded. The process thus allows more cost effective production of materials such as **bicalutamide.**
Dwg.0/3

FS CPI
FA AB; GI; DCN
MC CPI: B06-H; B07-H; B10-A10; B10-A15; B10-D03; B14-H01B
TECH UPTX: 20010628
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred process: the resolution step comprises resolving the intermediate compound of formula (I) by **crystallization** or high performance liquid chromatography.
Resolution by **crystallization** comprises contacting (I) with a chiral base to give a diastereomeric mixture of a chiral salt, resolving the mixture by **crystallization** and recovering a pure enantiomer of (I). The chiral base is especially (-)-cinchonidine. The solvent system used for resolution by **crystallization** is especially a mixture of methylene chloride and diethyl ether, most especially a mixture of 1-40 volume % of methylene chloride and 60-99 vol. % of diethyl ether. For production of **bicalutamide**, an intermediate compound (I; R1 = Me, R2 = CH2, R3 = a bond, R4 = 4-fluorophenyl and X1 = SO2) is resolved as outlined above, then the resolved compound can be reacted with a compound of formula (II) to give a pure enantiomer of **bicalutamide**
.
R7 = perfluoroalkyl.
ABEX UPTX: 20010628
EXAMPLE - In a typical process, the salt of an (R,S)-hydroxyacid and (-)-cinchonidine was formed by mixing a solution of the hydroxyacid (1 equivalent) with a solution of (-)-cinchonidine (1 equivalent). The cinchonidine was typically dissolved in chloroform while the acid was dissolved in, e.g., chloroform, methylene chloride, ethyl acetate or ethanol. The mixture was then stirred at room temperature overnight. The solvent was then removed by rotary evaporation. The salt (typically 20 mg) was then placed in a vial and treated with ethyl ether (2 ml). Methylene chloride was then added, with shaking, until all of the salt had been solubilized. The solution was then placed at 4 degrees C for **crystallization.** After **crystallization**, the supernatant was removed. The **crystals** were then dissolved in deuterated chloroform. The ratio of (R)- to (S)-enantiomer could then be assayed by integration of the fluorine signal using 19F NMR.

L106 ANSWER 19 OF 19 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1995-269262 [35] WPIX
DNC C1995-122047
TI Treating prostate cancer or androgen-associated conditions - using R-(-)-**casodex**, having reduced side-effects compared with racemate, also

e.g. for treating acne.
DC B05
IN GRAY, N M
PA (SEPR-N) SEPRACOR INC
CYC 58
PI WO 9519770 A1 19950727 (199535)* EN 23 A61K031-275
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KR KZ LK LR LT LU LV MD MG MN MW MX NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN
AU 9516873 A 19950808 (199545) A61K031-275
EP 748220 A1 19961218 (199704) EN A61K031-275
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 09508125 W 19970819 (199743) 19 A61K031-275
EP 748220 A4 19970910 (199815) A61K031-275
AU 9935074 A 19990819 (199945) A61K031-275
US 5985868 A 19991116 (200001) A61K031-275
ADT WO 9519770 A1 WO 1995-US871 19950120; AU 9516873 A AU 1995-16873 19950120; EP 748220 A1 EP 1995-908626 19950120, WO 1995-US871 19950120; JP 09508125 W JP 1995-519702 19950120, WO 1995-US871 19950120; EP 748220 A4 EP 1995-908626 19950120; AU 9935074 A Div ex AU 1995-16873 19950120, AU 1999-35074 19990616; US 5985868 A Cont of US 1994-184383 19940121, Cont of US 1996-662043 19960612, US 1998-107628 19980630
FDT AU 9516873 A Based on WO 9519770; EP 748220 A1 Based on WO 9519770; JP 09508125 W Based on WO 9519770
PRAI US 1994-184383 19940121; US 1996-662043 19960612; US 1998-107628 19980630
REP 4.Jnl.Ref; US 4636505; WO 9100733; 6.Jnl.Ref; DE 4318371
IC ICM A61K031-275
ICS A61K009-00; A61K009-20; **A61K009-48**; C07C317-46
AB WO 9519770 A UPAB: 19950905
Treatment of prostate cancer or conditions supported by androgens or caused by elevated androgen levels (especially benign prostatic hypertrophy or hyperplasia, acne or hirsutism), in a human comprises admin. of R-(-) **casodex** (I), free of the (+)-stereoisomer. Also claimed is a pharmaceutical compsn. containing a therapeutic amount of (I) free of the (+)-stereoisomer. (I) is (-)-N-(4-cyano-3-(trifluoromethyl)-phenyl)-3-((4-fluorophenyl)sulphonyl)-2-hydroxy-2-methylpropanamide.
ADVANTAGE - (I) shows potent, selective peripheral androgen antagonist activity, and has markedly reduced adverse side-effects due to central antiandrogen activity (e.g. gynaecomastia, breast tenderness, hot flushes, nausea, vomitting, bone pain, confusion, constipation, headache, diarrhoea, dyspepsia, fatigue, dizziness, rash and alterations of serum testosterone, oestradiol and LH) compared with racemic **casodex** (described in US4636505).
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B10-A10; B14-D02A; B14-H01B

=> d his

(FILE 'HOME' ENTERED AT 08:12:56 ON 12 MAY 2005)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 08:13:05 ON 12 MAY 2005
E BICALUTAMIDE/CN
L1 1 S E3
E C18H14F4N2O4S/MF
L2 3 S E3 AND 2/NR
L3 3 S L1,L2
SEL RN

```
L4            0 S E1-E3/CRN

     FILE 'HCAPLUS' ENTERED AT 08:14:50 ON 12 MAY 2005
L5          452 S L3
L6          581 S BICALUTAMID? OR CASODEX OR ICI176334 OR ZD176334 OR (ICI OR Z
L7          594 S L5,L6
L8            2 S L7 AND CRYS?/SC,SX
L9           16 S L7 AND ?CRYS?
L10           8 S L7 AND POLYMORPH?
                E POLYMORPH/CT
L11           3 S L7 AND (E19+OLD,NT,PFT,RT OR E20+OLD,NT,PFT,RT)
L12           1 S L7 AND E19-E29
                E E20+ALL
L13           9 S L7 AND (E13+OLD,NT,PFT,RT OR E14+OLD,NT,PFT,RT OR E15+OLD,NT,
                E E1+ALL
L14          12 S L7 AND E1+OLD,NT,PFT,RT
L15          27 S L7 AND (E396+OLD,NT,PFT,RT OR E397+OLD,NT,PFT,RT OR E398+OLD,
L16          55 S L7 AND (E405+OLD,NT,PFT,RT OR E411+OLD,NT,PFT,RT OR E412+OLD,
                E CRYSTALLIN/CT
L17           0 S L7 AND E10-E13
L18           0 S L7 AND E7+OLD,NT,PFT,RT
                E L7 AND E14+OLD,NT,PFT,RT
                E CRYSTALLIN/CT
L19           0 S L7 AND (E14+OLD,NT,PFT,RT OR E45+NT,PFT,RT)
L20           6 S L7 AND E49+OLD,NT,PFT,RT
L21           6 S L7 AND (E85+OLD,NT,PFT,RT OR E88+OLD,NT,PFT,RT OR E91+OLD,NT,
L22          79 S L8-L21
L23           1 S US20040063782/PN OR (US2003-660775# OR US2003-470223# OR US20
                E WESTHEIM R/AU
L24           2 S E4,E5
                E SYNTHON/PA,CS
L25          62 S E3-E32
L26           3 S L23-L25 AND L7
L27           2 S L26 AND L22
L28           1 S L26 NOT L27
L29           3 S L27,L28
                E PULVERIZ/CT
L30           2 S L7 AND E4+OLD,NT,PFT,RT
                E GRANULATION/CT
L31           2 S L7 AND E3+OLD,NT,PFT,RT
                E E14+ALL
L32          80 S L30,L31,L22
L33           2 S L7 AND ?AMORPH?
                E AMORPH/CT
L34           5 S L7 AND (E15+OLD,NT,PFT,RT OR E22+OLD,NT,PFT,RT)
L35           5 S L7 AND E150+OLD,NT,PFT,RT
L36           0 S L7 AND (E161+OLD,NT,PFT,RT OR E162+OLD,NT,PFT,RT OR E163+OLD,
L37          80 S L32-L35
L38           2 S L23-L25 AND L37
L39           3 S L29,L38
L40          50 S L37 AND (PD<=20020927 OR PRD<=20020927 OR AD<=20020927)
L41          49 S L40 NOT L39
L42          52 S L3(L)PREP+NT/RL OR L3(L)PROC+NT/RL OR L3/P
L43          10 S L41 AND L42
L44           4 S L43 AND CRYS?
L45           2 S L44 AND CRYS?/TI
L46           5 S L39,L45
L47          39 S L41 NOT L42-L46
                SEL DN AN 7 22
L48           2 S L47 AND E1-E6
L49           7 S L46,L48
L50          19 S L7 AND RACEM?
L51          16 S L50 AND (PD<=20020927 OR PRD<=20020927 OR AD<=20020927)
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L52          14 S L51 NOT L49
                SEL DN AN 2 4 5
L53           3 S E7-E13 AND L52
L54          10 S L49,L53 AND L5-L53
L55           7 S L7 AND (ETHYLACETATE OR ETHYL ACETATE OR ETOAC)

     FILE 'REGISTRY' ENTERED AT 08:44:11 ON 12 MAY 2005
L56           1 S 141-78-6

     FILE 'HCAPLUS' ENTERED AT 08:44:16 ON 12 MAY 2005
L57           6 S L7 AND L56
L58           7 S L55,L57
L59           4 S L58 AND L54
L60          10 S L54,L59
L61           3 S L58 NOT L60
                SEL DN AN 1
L62           1 S E14-E16 AND L61
L63          11 S L60,L62

     FILE 'REGISTRY' ENTERED AT 08:45:48 ON 12 MAY 2005
L64           1 S 63-42-3
L65           1 S 9004-65-3
L66           1 S 9005-25-8
L67           1 S 10103-46-5
L68           1 S 9004-34-6
L69          13 S 7664-38-2/CRN AND CA/ELS AND 2/NC NOT (MXS OR PMS OR IDS OR M
L70          11 S L69 NOT 45CA?
L71        6830 S 9004-34-6/CRN
L72        2208 S 9005-25-8/CRN

     FILE 'HCAPLUS' ENTERED AT 08:48:07 ON 12 MAY 2005
L73          14 S L64-L68,L70-L72 AND L7
L74          10 S L73 AND (PD<=20020927 OR PRD<=20020927 OR AD<=20020927)
L75           1 S L74 AND L63
L76          11 S L63,L75
L77           9 S L74 NOT L76
                SEL DN AN 2 3 4 5
L78           4 S L77 AND E17-E28
L79          15 S L76,L78 AND L5-L55,L57-L63,L73-L78

     FILE 'REGISTRY' ENTERED AT 08:51:02 ON 12 MAY 2005

     FILE 'HCAPLUS' ENTERED AT 08:51:15 ON 12 MAY 2005

     FILE 'WPIX' ENTERED AT 08:52:02 ON 12 MAY 2005
L80         169 S L6/BIX
                E BICALUTAMIDE/DCN
                E CASODEX/CN
                E CASODEX/DCN
                E BICALUTAMIDE/CN
L81           1 S E3
                E RA1M70/DCN
L82           1 S E3-E5
L83           1 S (N 4 CYANO 3 TRIFLUOROMETHYL PHENYL 3 4 FLUORO BENZENESULFONY
L84         170 S L80,L82,L83
                E RA1M7O/DCN
L85         131 S E3-E13
L86         180 S L84,L85
L87          18 S L86 AND ?CRYS?/BIX
L88           1 S L85 AND ?POLYMORPH?/BIX
L89           0 S L85 AND ?POLY MORPH?/BIX
L90           4 S L85 AND ?AMORPH?/BIX
L91           7 S L86 AND R032/M0,M1,M2,M3,M4,M5,M6
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L92            3 S L86 AND (B12-M11H OR C12-M11H)/MC
L93           11 S L86 AND (A61K009-50 OR A61K009-14 OR A61K009-16)/IPC
L94           26 S L87,L88,L90-L93
                 E WESTHEIM R/AU
L95            2 S E4
                 E SYTHON/PA
                 E SYNTHON/PA
L96           62 S E3-E10
L97            3 S L86 AND L96,L96
L98            2 S L94 AND L97
L99            4 S L86 AND A61K009-48/IPC
L100          28 S L94,L99
L101           2 S L97 AND L100
L102           3 S L97,L101
L103          26 S L100 NOT L102
                 SEL DN AN 1 2 3 7 18 19 22 23 24 25
L104          16 S L103 NOT E1-E20
L105          19 S L102,L104
L106          19 S L105 AND L80-L105

    FILE 'WPIX' ENTERED AT 09:13:09 ON 12 MAY 2005

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